DOES NOT CIRCULATE

ANNUAL MEETING: TORONTO, JUNE 20-24

UNIVERSITY OF MICHIGAN
MAY 25 1955
MEDICAL LIBRARY

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY MAY 7 1955

TABLE OF CONTENTS

Some Problems in the Study of Cancer in Man Sir ERNEST KENNAWAY, D.M., D.SC., F.R.C.P., F.R.S. 1107
Smoking and Chewing of Tobacco in Relation to Cancer of the Upper Alimentary Tract L. D. SANGHVI, PH.D., K. C. M. RAO, M.SC., and V. R. KHANOLKAR, M.D. 1111
Cigarette Smoking and Bronchial Carcinoma D. A. PYKE, M.B., M.R.C.P. 1115
Physiological Principles in the Treatment of the Unconscious Patient WILLIAM W. MUSHIN, M.B., F.F.A. R.C.S., D.A. 1116
Treatment of Leukaemia and Allied Disorders with 6-Mercaptopurine JAMES R. FOUNTAIN, M.B., M.R.C.P.Ed. 1119
Erythraemic Myelosis Terminating in Erythroleukaemia J. R. HINDMARSH, M.D., M.R.C.P., and T. A. J. WICKHAM, M.B. 1124
Some Advances in the Surgery of the Oesophagus R. H. FRANKLIN, F.R.C.S. 1126
Amyloidosis in Rheumatoid Arthritis, and Significance of "Unexplained" Albuminuria GEORGE R. FEARNLEY, M.D., M.R.C.P., and RITA LACKNER, M.D., M.R.C.P. 1129
Malarial Therapy in the Nephrotic Syndrome A. G. SHAPER, M.B., D.T.M.&H. 1132

MEDICAL MEMORANDA
Fatal Case of Pernicious Anaemia Associated with Chloramphenicol Treatment. M. A. PEYMAN, B.M., M.R.C.P. 1135
Accidental Poisoning with Tetrachlorethane. J. M. WARD, M.R.C.S. 1136

BOOK REVIEWS 1137

REFRESHER COURSE
Ante-partum Haemorrhage. FRANK STABLER, M.D., F.R.C.S., F.R.C.O.G. 1145

GENERAL ARTICLES AND NEWS
PUBLIC HEALTH AND PREVENTIVE MEDICINE 1147
EMPIRE RHEUMATISM COUNCIL 1148
GENERAL ELECTION: MEDICAL CANDIDATES 1149
HEALTH AND POLITICS 1150
IMPERIAL CANCER RESEARCH FUND 1150
MEDICAL NOTES IN PARLIAMENT 1163
MEDICO-LEGAL 1164
MEDICAL NEWS 1166
QUESTIONS AND COMMENTS 1168

OBITUARY
Egbert Morland, M.D., F.R.C.P., F.R.C.S. 1159
D. T. Barry, M.D., D.SC., F.R.C.S. 1161
D. W. Hoodless, O.B.E., B.SC., L.M.S.S.A. 1161
J. C. Pearce, M.D. 1162

LEADING ARTICLES
New Work on Transplantation 1139
Cycloserine 1140
Health Services in India 1141

ANNOTATIONS
Public Health Salaries 1142
Cancer and Thyroid Activity 1142
Nomenclature and Morbidity Surveys 1143
Paralysis Following Poliomyelitis Vaccination 1144

CORRESPONDENCE
Youth Looks at General Practice. G. F. G. MARSHALL, M.B. 1153
Cancer of Breast. R. MORRISON, M.D., F.F.R. 1153

SUPPLEMENT
Full Contents on First Page of Supplement
The Law on Mental Illness and Mental Deficiency 211
Remuneration in Public Health Service 214
Joint Annual Meeting: Programme 215
Correspondence:
Rewards for Skill. M. W. BIRD, M.R.C.S. 222
Entry into Practice. G. H. ROSSDALE, D.M. 223

CORRESPONDENCE—*contd.*
Carcinoma and Tuberculosis. D. L. CALDWELL, M.R.C.P. 1154
Natural Childbirth. HAZEL B. BAKER, M.B.; RACHEL LITTLEWOOD 1154
Salk Vaccine. J. G. HUMBLE, M.R.C.S. 1154
Hysterectomy. W. G. MILLS, F.R.C.S.; L. MARTINDALE, F.R.C.O.G. 1155
Chlorpromazine. J. A. R. BICKFORD, M.R.C.S. 1155
Toxicity of Chlorpromazine. J. H. OWEN, M.B.; B. V. EARLE, M.D. 1155
Cyst Following Hernia Repair. G. T. WATTS, F.R.C.S. 1156
Chicken-pox. S. G. ASKEY, M.D.; J. J. LINEHAN, M.D. 1156
Corrosive Poisoning. H. TERRY, M.B. 1157
Pesticides. A. F. McK. JACKSON, B.SC. 1157
Enuresis L. A. NICHOLS, M.R.C.S. 1157
E.C.T. in Pregnancy. R. J. RUSSELL, M.R.C.S., and L. G. M. PAGE, M.R.C.S. 1157
Speaking Up. L. FISCH, M.D., D.L.O. 1157
An Occupational Hazard. EDITH FAULKNER, M.B. 1158
Swallowed Hair-grips. MARGARET S. I. WILLIAMS, M.B. 1158
Appendicitis. J. W. WESTON, M.R.C.S. 1158
Thermometers. P. GILBERT, M.B. 1158
Anonymous Anaesthetists. J. A. ROSS, F.R.C.S.Ed. 1158

Vital Statistics 1164

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4922, WEEKLY, PRICE 3/-

Copyright

REGISTERED AS A NEWSPAPER

CASSELL MEDICAL BOOKS

MANUAL OF MEDICAL HELMINTHOLOGY

By C. J. HACKETT, M.D., F.R.C.P.,
with the co-operation of
Professor J. J. C. BUCKLEY, D.Sc.,
and the late
Professor J. MURGATROYD, M.D., F.R.C.P.

This practical new book, which is based on the helminth exhibits of the Wellcome Museum of Medical Science, is designed especially for doctors in the tropics. It contains detailed descriptions of the important helminths—Trematoda, Cestoda, and Nematoda. Some thirty parasites are described in full together with the illnesses they cause in man.

This forms the main body of the text, but there is in addition a general introduction to helminthic diseases; and general sections on the Trematoda, Cestoda and Nematoda are followed by a discussion of the clinical manifestations of helminthiasis, clinical and laboratory diagnosis, and general remarks on treatment, prognosis and prevention.

Special attention has been paid to the preparation of the illustrations, which aim at simplifying the problems of identification which confront the worker in this field. *Illustrated.* **18s. 6d.** *net*

37/38 St. Andrew's Hill, London, E.C.4

J. & A. CHURCHILL LTD.

HIGH BLOOD PRESSURE
By G. W. PICKERING, M.A., M.B., F.R.C.P.
106 Illustrations (5 in Colour). *Ready Shortly.* About 63s.

FORENSIC MEDICINE
A Textbook for Students and Practitioners
By Sir SYDNEY SMITH, C.B.E., M.D., F.R.C.P., and F. S. FIDDES, O.B.E., M.B.
New (Tenth) Edition. 173 Illustrations. *Ready Shortly.* About 37s. 6d.

RECENT ADVANCES IN RADIOLOGY
New (Third) Edition. By THOMAS LODGE, M.B., F.F.R., D.M.R.
182 Illustrations. About 45s.

DISEASES OF THE LIVER
By MITCHELL A. SPELLBERG, M.D., F.A.C.P., University of Illinois.
96 Illustrations (2 in Colour). 128s.

DISORDERS OF THE BLOOD
Diagnosis, Pathology, Treatment and Technique
By Sir LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P., D.P.H., and C. J. C. BRITTON, M.D., D.P.H.
Seventh Edition. 20 Plates (12 coloured) and 106 Text-figures. 63s.

THE HAEMOLYTIC ANAEMIAS
Congenital and Acquired
By J. V. DACIE, M.D., M.R.C.P.
98 Illustrations. 50s.

CURRENT CONCEPTS IN DIGITALIS THERAPY
A Guide to the use of Digitalis Drugs
By BERNARD LOWN, M.D., and SAMUEL A. LEVINE, M.D., Harvard Medical School
21 Illustrations. 15s.

THE RADIOLOGY OF BONES AND JOINTS
An Introduction to the Study of Tumours and other Diseases of Bone
By JAMES F. BRAILSFORD, M.D., F.R.C.P., F.I.C.S.
Fifth (Enlarged) Edition. Over 725 Illustrations. 90s.

THE NORMAL CHILD
Some Problems of the First Three Years and Their Treatment
By R. S. ILLINGWORTH, M.D., F.R.C.P.
64 Illustrations. 30s.

RECENT ADVANCES IN SURGERY
Fourth Edition. Edited by HAROLD EDWARDS, C.B.E., M.S., F.R.C.S.
157 Illustrations. 40s.

RECENT ADVANCES IN PAEDIATRICS
By various authors under the Editorship of DOUGLAS GAIRDNER, D.M., F.R.C.P.
117 Illustrations. 42s.

104 GLOUCESTER PLACE, LONDON, W.1

HENRY KIMPTON'S PUBLICATIONS

New (4th) Edition — Now Ready
DISEASES AFFECTING THE VULVA
By ELIZABETH HUNT, B.A., M.D., Ch.B.(Liverpool)
FOURTH EDITION, REVISED AND ENLARGED
6 in. × 9½ in. Cloth — 236 Pages — 47 Illustrations and 17 Coloured Plates — Price 31s. 6d. net (Postage 9d.)

New Book — Just Ready
PULMONARY DISEASES
Edited by ROSCOE L. PULLEN, A.B., M.D.
With Twenty Contributors
6 in. × 9½ in. Cloth — 669 Pages. — 195 Illustrations and 4 Plates, 1 in Colour. — Price £5 10s. net

New (8th) Edition — Now Ready
DISEASES OF THE SKIN
By OLIVER S. ORMSBY, M.D.
and HAMILTON MONTGOMERY, M.D., M.S.
EIGHTH EDITION, REVISED AND ENLARGED
6 in. × 9½ in. Cloth — 1,503 Pages — 750 Illustrations — 11 Coloured Plates — Price £8 net

New (6th) Edition — Now Ready
CARE OF THE AGED (GERIATRICS)
By MALFORD W. THEWLIS, M.D.
SIXTH EDITION, REVISED AND ENLARGED
6½ in. × 10 in. 832 Pages 155 Illustrations Cloth Price £5 12s. 6d. net

New (3rd) Edition — Now Ready
PRACTICE OF ALLERGY
By WARREN T. VAUGHAN, M.D.
THIRD EDITION, REVISED BY J. HARVEY BLACK, M.D.
7 in. × 10 in. 1,164 Pages 335 Illustrations Cloth Price £7 17s. 6d. net

HENRY KIMPTON
25 Bloomsbury Way London, W.C.1
Medical Book Department of Hirschfeld Brothers Ltd.

ZOPLA

MEDICAL AND SURGICAL PLASTERS

Developed in collaboration with some of the leading hospitals, the ZOPLA range of self-adhesive, zinc oxide plasters covers every medical, surgical, and dermatological need.

The range includes :

STRAPPINGS — for surgical use. Powerfully adhesive, on white, flesh, and elastic cloths.

FELTS of selected Merino Wool, for all padding and protective purposes. Only pure wool felt will retain its resilience and will not harden in use.

HELVIA—First Aid Flexible Dressing—elastic adhesive plaster with medicated gauze.

ZOPLA-BANDS—Elastic adhesive bandage of superior quality.

Details of the full ZOPLA range, together with samples, will gladly be sent on request.

LESLIES LIMITED
ESTABLISHED 1823
Walthamstow, London, E.17

BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 7 1955

SOME PROBLEMS IN THE STUDY OF CANCER IN MAN

BY

Sir ERNEST KENNAWAY, D.M., D.Sc., F.R.C.P., F.R.S.

From the Department of Pathology, St. Bartholomew's Hospital, London

Cancer research is now unavoidably divided into two sections: (*a*) *fundamental*, which looks for an answer to the question "Why, and how, does a cell divide?"; and (*b*) *empirical*, which seeks to identify carcinogenic factors which we can avoid. The first of these has passed wholly into the field of physics and chemistry and requires the most refined methods, both technical and theoretical, of those subjects. To many persons, distressed by the mortality from cancer, progress may seem very slow, but they should remember that the full application of biophysics to the problem is of very recent growth, and that whole areas of knowledge which we do not yet possess may be required for success. No doubt Wellington could have saved a great number of British lives at Waterloo by the discreet use of an atomic bomb of very modest dimensions before the armies engaged, but the requisite technique simply did not exist.

The present paper brings together some of those questions in purely empirical cancer research which seem to be ready for further inquiry. However anxious we may be to simplify the problem of cancer, we must recognize that it is inherently complex because the animal body itself is complex. Even when a reasonably satisfactory answer can be given to the fundamental question "Why, and how, does a cell divide?" the application of this knowledge to the very peculiar distribution of cancer by sex and organ must present many problems.

Cancer of the Cervix and Circumcision

The view is now advocated that the association between cancer of the cervix and non-circumcision of the male (Wynder *et al.*, 1954; Wynder, 1955) is due to transference of carcinogenic smegma in the act of intercourse, a process which would be identical in nature with a mouse-painting experiment. Whatever one may think of the likelihood of this explanation, it certainly offers a remarkable instance of the specificity of carcinogens for different tissues. In England and Wales in 1945 there were 4,039 deaths attributed to cancer of the uterus other than of the corpus; if any large fraction of these was due to application of smegma it is remarkable that in the males, where the contact of this material with the epithelium is intimate and continuous, there were only 132 deaths from cancer of the penis, though some other cases may have been cured by surgery.

A causal connexion between cancer of the cervix and non-circumcision was suggested first by W. Sampson Handley (1936), who wrote of "marital infection with the sub-preputial flora" and seemed to think of this factor as sufficient in itself and as already proved. Such certainty is quite unwarranted, because we do not know (1) that the vaginal flora is in fact altered, although this question is quite accessible to investigation; or (2) whether any such alteration is pro- or anti-carcinogenic.

The use of a condom protects the cervix from any transfer of carcinogenic material from the male more effectually than does any other method, and in theory provides the ideal experiment for settling this question, but actually it is difficult to ascertain the constancy of the practice over a number of years.

Cancer of the Cervix in Jewish Women

The low incidence of cancer of the cervix in Jewish women is established by a number of investigations. The literature up to 1947 was summarized (Kennaway, 1948) and much confirmatory material has been published since then (Wynder *et al.*, 1954).)

Various possible explanations have been suggested, of which one is the Jewish law relating to menstruation. A section (Niddah) of the Talmud, consisting of 10 chapters, forbids coitus during the flow, and for not less than five days, and for seven days afterwards, hence the whole period of abstention is $n+7$ days and n is never less than 5. Under normal conditions, abstention for 12 days would allow resumption near the time of ovulation, of which process those who laid down this rule of course knew nothing (for further details see Kennaway, 1948).

To assume that the law of Niddah is, for all practical purposes, obsolete, is easy, and this solution of the question is often put forward and sometimes seems to be welcome. But such matters of purely private conduct need very careful inquiry. The lack of any adequate investigation from Jewish sources is perhaps not very surprising. To the orthodox believer all such laws are the direct expression of God's wisdom, and human approval or disapproval of them is wholly irrelevant, while to one of the modern school they are elements of a primitive religion with which he may not wish to be associated. But any attempt to gain from this source more knowledge is surely in no way inconsistent with the belief that the practice is of Divine institution. All recent work upon cancer of the cervix (the literature is reviewed by Wynder *et al.*, 1954) indicates that marriage, apart from child-bearing, and especially early marriage, increases the liability, while the celibate life of nuns (Gagnon, 1950) gives protection. By "marriage" in this sense one means, not any civil or religious state, but coitus. Between these two extreme conditions of early marriage and virginity there is surely the bare possibility that the partial abstention enjoined by the law of Niddah gives partial immunity. At any rate, the question is worth investigation; and why can it not be settled one way or the other in the next year or two?

Any idea that the law of Niddah is now an almost forgotten matter, of merely antiquarian interest, is simply

untrue. In London, at any rate, a Jewish girl whose engagement is announced in the Press receives from one or other of certain Jewish societies a simple, practical, and forcible statement of the law, and often this is her first acquaintance with it. How far these instructions are obeyed is of course another matter altogether, but those to whom they are of most concern cannot be ignorant of them even here at the present day.

There are at least two methods of investigating this question—namely, to ascertain (1) the proportion of women who obey any part of the relevant law in a Jewish community in which the incidence of cancer of the cervix can be ascertained, but the inquiry about obedience to the law must be a genuine one, not mixed up with any assumptions or general impressions; (2) the personal history of any Jewish woman who develops cancer of the cervix. This would appear to be the simplest and quickest method of approach, because the results in, say, a dozen cases might show whether this line was worth following, although such a number would be considered quite inadequate statistically. This method has been applied by Wynder *et al.* (1954), who obtained the following result (Table I).

TABLE I.—*Observance of Talmudic Law in 20 Cases of Cancer of the Cervix in Jewish Women (Wynder et al.)*

	Days' Abstinence after Menses
Class A: In 10 women	0
„ B: „ 5 „	5, 4, 3, 3, 2
„ C: „ 5 „	7

One may suggest that the value of these 20 cases as evidence is not uniform. Of the 10 women who practised no abstinence, 7 had intercourse with more than one partner, and hence one can believe that they were not scrupulous in obeying any part of the Talmudic law; whether the statements of the 5 women of Class C, that they observed the seven-days rule, are equally convincing, may be a matter of opinion. All the women in C and 3 of the 5 in Class B had one partner only. Wynder *et al.* (1954) ignore this aspect of the matter altogether and discuss only the data relating to age and circumcision, while Wynder (1955), in his most recent paper, says, without quoting any tabulated data, "Twenty Jewish cervical cancer cases do not suffice for statistical comparison, but they seem to be in line with the controls. Five of the 20 patients in this group did not abstain after menses." He does not explain the reduction from 10 to 5 of the non-abstaining cases. The relevant passage in his summary, "The abstinence period practised by orthodox Jewish women after the end of menses is not believed to be the basic factor accounting for the low incidence of cervical cancer among Jewish women," does not encourage further investigation.

Table I certainly indicates that further inquiry is very desirable. After all, one may not get a quite clear-cut result because all cases of cancer of the cervix may not have the same cause, just as all cases of cancer of the lung are not due to smoking. In any case, this one series of 20 cases cannot be held to settle the matter, and material for further inquiry must be available in Jewish practice in London. In both inquiries, (1) and (2) above, the truthfulness of the replies is, of course, vital, and it is therefore all-important that the women should not regard the questions as a moral inquisition. Probably the best interviewer would be a Jewish woman doctor.

Cancer of the Lung in Non-smokers

This process is of great importance as the background upon which the effects of smoking are superimposed. The number of deaths in both sexes attributed to cancer of the lung in England and Wales annually is now about 15,000. Doll (1953) considers that about one-fifth of these deaths —that is, about 3,000—are not due to tobacco. The consumption of tobacco, especially in the form of cigarettes, has increased considerably in the last 30 years, and hence any form of cancer due to smoking would be expected to increase also at some later period. We do not know the cause, or causes, of the 3,000 cases independent of tobacco, and therefore we have no reason to think that this factor has increased. Even if it has increased, it is extremely unlikely that it has done so in close parallelism to the increase in the consumption of tobacco. As we know nothing to the contrary, we may assume for the moment that this factor has not altered in, say, the last 30 years.

If this were so, the unknown factor would have produced about 3,000 cases every year during this period. But as recently as 1935, when the number of deaths was 3,195, this source would have supplied the whole number which occurred, and, proceeding backwards, the total falls to 612 in 1922 at the beginning of the 30-year period (Fig. 1). It is

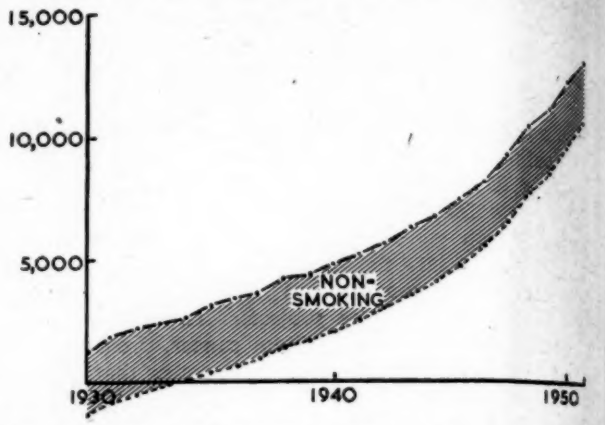


FIG. 1.—Deaths from cancer of lung. Males and females. England and Wales.

of course quite easy to invoke "defective diagnosis" as the sole explanation of any such process, whatever its magnitude or time-relations may be, and to attempt no further investigation, but any assumption that such errors are exactly adequate numerically for this purpose is purely arbitrary. The unknown factor may be (*a*) extrinsic or (*b*) intrinsic. (*a*) It is unlikely to be one of the known occupational factors which are carcinogenic to the lung (chromates, arsenic, nickel, asbestos, radioactivity), because these affect only small numbers of persons, chiefly of the male sex. (*b*) The absence of any sexual difference and the lack of any correlation with density of population suggest an intrinsic factor. The identification of this factor would be of very great interest.

No doubt the crude data shown in Fig. 1 require careful analysis in view of the considerable changes in the age structure of the population which have taken place in the last 30 years, but that is a matter for statisticians.

The proportion of non-smokers is important when the consumption of tobacco in different classes or countries—for example, Britain and Finland—is being compared. Thus in the latter country women appear to smoke very little, and hence the consumption "per head" falls very largely upon only one-half of the population.

In the long run it may appear that this sorting out of the cases not due to tobacco is the most valuable part of the immensely important contribution of Doll and Bradford Hill, and others, to cancer research; this same unknown factor may be the cause of malignant growth in other organs also. We can avoid the one factor, tobacco, if we wish, because we know what it is; we cannot avoid the other.

Deaths Attributed to Cancer of the Lung in Women

In England and Wales the increase in 1953 amounted to only 11 cases (Registrar-General, 1954), whereas the deaths of males showed an increase of the usual amount (891 cases). Of course, this halt may not persist, but, if it does so, the problem of the factors, perhaps first active many years ago,

which are concerned in this change will be very attractive, or, if one is then still expected to think that a very large part of the increase in deaths attributed to cancer of the lung is due to improved diagnosis, an explanation of this sexual difference must be found.

Histological Characters of Cancer of the Lung

These cancers show about five different types, which may differ in aetiology. Hence when one compares the total incidence of cancer of the lung upon different populations and countries one may be concealing important differences in the proportions of these types. Recently Kreyberg (1954) has emphasized the importance of this question. The practical difficulty is to obtain data from large numbers of unselected cases in which the diagnosis has been made by competent histologists, and some experienced observers are doubtful about the value of such classifications on the ground that more than one type may occur in the same lung.

Systemic Effects of Tobacco

The obvious method by which tobacco smoke can have a carcinogenic effect is by the arrest of the droplets of which it is composed upon the bronchial mucous membrane. But the inspiration of this smoke has such powerful systemic effects that one wonders whether these may possibly play a part also. The discharge from the posterior pituitary has so strong an antidiuretic effect (Walker, 1949) that the comment has often been made that one wonders how some cigarette smokers pass any urine at all (Fig. 2).

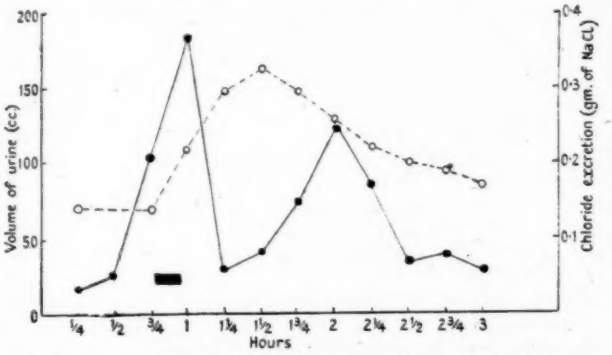


FIG. 2.—Systemic effect of tobacco. The subject drank 900 ml. of water at zero. He emptied his bladder at 15-minute intervals. The continuous line shows the volume of urine excreted. After 45 minutes he smoked one cigarette, which produced the inhibition shown in the graph. The broken line shows the total chloride excretion. Note the rise in total chloride coincident with the inhibition (Walker, 1949). Reproduced by permission of Dr. Walker and the *Quarterly Journal of Medicine*.

This secretion of the posterior pituitary is also broncho-constrictor, and this action might slow down the inspiratory current and thus favour the deposition of particles, but so far no such effect of smoking has been demonstrated. Dr. H. G. J. Herxheimer, of University College Hospital, London, very kindly subjected two smokers to a test with his apparatus which measures resistance to expiration, and could find no effect. But possibly other systemic effects might be worth consideration.

Amount of Cancer

When the occurrence of cancer in different populations is compared, the incidence may be found to fall more or less upon one or another organ, while the total number of individuals remains about the same whatever the organ or organs chiefly affected. There seems in these cases to be something that may be regarded provisionally as an "amount" of cancer, and the anatomical distribution of this "amount" is variable (E. L. and N. M. Kennaway, 1937).

"There appears to be a general law that when in a given population the incidence of cancer in one particular organ is markedly increased as compared with another population, there is then a compensating decrease in the incidence of cancer in a number of other organs. As a result, the incidence of cancer in different populations, whether of the same sex or not, may represent a very different distribution over the various organs or tissues, but the sum total—the total incidence of cancer—remains on an even level. This phenomenon shows that the development of malignancy in a given site, although in itself a strictly localized process, is conditioned by factors lying outside the site, which may therefore be called 'general' or 'systemic' factors" (Cramer, 1931).

This phenomenon was described first by Snijders and Straub (1924) in Sumatra; a small selection from their results is given in Table II.

TABLE II.—*Incidence of Primary Cancer of the Liver in Sumatra, and in England and Wales (Snijders and Straub)*

	Javanese Men	Corresponding Group from Dutch Statistics	Javanese Women	Corresponding Group from Dutch Statistics
Mortality from cancer per 100,000 per year	26·6	24·3	25·4	24·5
		England and Wales, 1931		England and Wales, 1931
Primary cancer of liver % of all cancers ..	84	4·8	22·2	4·7

Perhaps the simplest instance of the "amount" of cancer is afforded by a comparison of cancers in the two sexes in the same country (Table III).

TABLE III.—*Deaths from Carcinoma, 1940-2. England and Wales (General Register Office)*

Males		Females	
Cancers of male reproductive organs ..	7,172	Cancers of female reproductive organs ..	38,916
Scrotum, prostate, testis, penis, etc.	7,009	Uterus, ovary, tubes, vulva, vagina, etc...	18,867
Breast	163	Breast	20,049
Other organs	82,730	Other organs	58,090
Total ..	89,902	Total	97,006
Excess of cancers in females ..	7,104		

For instance (Table III), the total deaths from carcinoma in males (89,902) and females (97,006) show a difference of only about 7%, yet the latter total includes 38,916 deaths, or 40% of the whole, from carcinoma of organs peculiar to the female, among which organs the female breast, being capable of lactation, must for the present purpose be reckoned.

One wishes that statisticians would some day examine this matter and tell us to what extent the figures merely illustrate the fact that a person who dies of a disease A does not die of a disease B. But it is difficult to believe that that is all that can be said about it.

Localization of Malignant Growth

This extremely important subject seems to attract very few investigators, probably because it does not promise to yield quickly that "something to publish" which assures renewal of annual grants and is the bane of cancer research.

Cancer of the breast causes the death of about 7,300 women in England and Wales per annum. If one omits the other cases cured by surgery and divides this number by 365, one finds that every day only about 20 of the 13½ million women aged 30 and over begin to develop this form of cancer. Moreover, in the great majority of these, the disease begins in one of the two breasts, and at one small area in this glandular organ of considerable size. Hence the importance of localizing factors is obvious, but we know hardly anything about them. In recent years much has been learned about hormonal factors in relation

to the breast, but these are distributed in the blood stream and there is no apparent reason why their action should be localized. Such considerations apply also to some forms of cancer of the lung where substances introduced and dispersed with the inspired air represent the hormonal factors in the case of the breast.

Possibly every case of cancer arises from the conjunction of a number of factors, as yet unknown to us, at one spot. Those who think that the carcinogenic action of, for instance, cholesterol (Hieger and Orr, 1954) can be ignored because this compound is "a normal constituent of the body" show little comprehension of biochemical matters. The highly dangerous properties of another normal constituent—namely, potassium—are kept under control only by the balance of other factors.

Incidence of Cancer in Town and Country

A number of investigations have shown, with varying degrees of distinctness, a higher incidence of various forms of cancer among town dwellers. In seeking for a reason, the fact that better methods of diagnosis are more accessible in towns is always easy to invoke and difficult to assess. Where the respiratory tract is concerned one must of course consider atmospheric pollution and exposure to soot containing at least one carcinogen—namely, 3:4-benzpyrene (Stocks, 1936, 1953; E. L. and N. M. Kennaway, 1951; Curwen *et al.*, 1954). But does this latter factor affect any other parts of the body? Cancer of the scrotum is rare in agricultural workers and is almost unknown in those social classes who wash most (E. L. and N. M. Kennaway, 1946). Thirty years ago the suggestion was made that "it would seem possible that cancer of the scrotum is influenced by exposure to coal-smoke—in other words, possibly all town dwellers are in some very slight degree liable to "chimney-sweep's cancer" (Kennaway, 1925). A complete survey is required of the incidence of every form of cancer upon dwellers in rural districts, and in the various grades of urban areas, in which every effort is made to discriminate between the effects of better diagnosis, and of town smoke; the latter factor is remediable by methods already in existence. Probably various carcinogens, with the exception of sunlight, are more abundant in towns and their actions may summate, a process about which we know very little; the latest contribution on this question is that of Cloudman *et al.* (1955).

Cancer and the Consumption of Milk

Cow's milk contains a carcinogenic factor in the non-saponifiable fraction, as do various human organs (Hieger, 1949), and, as a constituent of diet, has a protective action against some forms of cancer (Hoch-Ligeti, 1952). The consumption of milk by man shows great differences in different countries, dependent upon a variety of factors such as the character of pasture, the tsetse fly, sexual and social taboos and conventions, and so on. In some parts of Africa the numerous cattle are not regarded as sources of milk, nor of meat, but as currency, especially for the purchase of wives. In some areas milk is taboo for men, as it was in effect in this country not very long ago (Kennaway, 1951). The numerous travellers in Tibet who write books always emphasize the abundance of Yak butter, while Australasia had no source of milk until the nineteenth century. Even countries in Europe show considerable differences in this respect; thus the daily consumption of milk is high in Finland (Kennaway, 1954), being about 1.34 pints per head as against 0.72 pint in the United Kingdom.

Anyone wishing to make a literary investigation of this matter would find a great quantity of data scattered through official and other publications; the results might or might not show any correlation with any forms of cancer, and could of course be used in the study of any other diseases also. Two valuable publications are those of the Food and Agriculture Organization of the United Nations (1952, 1953).

A Suggestion

Cancer research, like other branches of science, is tending to be buried under its own literature. Those whose business it is to attempt to keep a watch upon this literature know that many investigations are reported which appear to promise further results, and yet, in say ten years' time, if they are remembered at all, they are found to have had no progeny. This may be because they are inherently infertile, or because the investigator has been diverted to other matters which appear more productive of results and annual grants: these forgotten researches are hidden, like coelacanths, beneath an ocean filled by other developments. Surely some persons should be appointed to pick over the literature of, say, the last 25 years in the light of later knowledge and to seek for anything worthy of resuscitation; they should hold a quite definite appointment with good remuneration, should be under no obligation to produce anything, and should be trusted to carry on their work efficiently without any compulsion to write endless reports about it. They will reject many researches because the technique was inadequate at the time or is shown by our later knowledge to have been so; but now and then something useful may be disinterred.

In 1945 J. C. Mottram described a greater yield of tumours of the skin of mice from 3:4-benzpyrene when applied at midnight than when applied at midday; he attributed this difference to greater mitotic activity at night, and did not consider any other possible diurnal differences in metabolism. This result indicates that the conditions during the first few hours after application determine the yield of tumours during the second and later months. At the present time research on cancer is much concerned with such periods of incubation. Thus, Nielsen and Clemmesen (1954), in a very short paper of great interest, have plotted figures for the mortality from cancer of the lung in 1950 against those for the consumption of cigarettes in 1930. Mottram's result is of such importance that one wonders whether the experiment has ever been repeated. He used only 6, and 24, mice in his two experiments, and made the day, and night, paintings on opposite sides of the same mouse, which is not the only possible, and perhaps not the best, procedure. A very experienced worker with whom I have discussed the result is very dubious about it. Those who knew Mottram, who died in 1945, will agree that, though he was far from infallible, his numerous ideas were always interesting; at heart he was much more a zoologist than a pathologist.

REFERENCES

Cloudman, A. M., Hamilton, K. A., Clayton, R. S., and Brues, A. M. (1955). *J. nat. Cancer Inst.*, **15**, 1077.
Cramer, W. (1931). *Z. Krebsforsch.*, **34**, 531.
Curwen, M. P., Kennaway, E. L., and Kennaway, N. M. (1954). *Brit. J. Cancer*, **8**, 181.
Doll, R. (1953). Ibid., **7**, 303.
Food and Agriculture Organization of the United Nations (1952). *Second World Food Survey*. Rome.
—— (1953). *Bulletin No. 24, Dairy Products*. Rome.
Gagnon, F. (1950). *Amer. J. Obstet. Gynec.*, **60**, 516.
Handley, W. S. (1936). *Lancet*, **1**, 987.
Hieger, I. (1949). *Brit. J. Cancer*, **3**, 123.
—— and Orr, S. F. D. (1954). Ibid., **8**, 274.
Hoch-Ligeti, C. (1952). *Tex. Rep. Biol. Med.*, **10**, 996.
Kennaway, E. L. (1925). *J. industr. Hyg.*, **7**, 69.
—— (1948). *Brit. J. Cancer*, **2**, 177.
—— (1951). *Middx Hosp. J.*, **51**, 144.
—— (1954). *Med. Press*, **232**, 520.
—— and Kennaway, N. M. (1937). *Acta Un. int. Cancr.*, **2**, 101.
—— —— (1946). *Cancer Res.*, **6**, 49.
—— —— (1951). *Brit. J. Cancer*, **5**, 153.
Kreyberg, L. (1954). Ibid., **8**, 199, 599, 605.
Mottram, J. C. (1945). *J. Path. Bact.*, **57**, 265.
Nielsen, A., and Clemmesen, J. (1954). *Danish med. Bull.*, **1**, 194.
Registrar-General (1954). *Statistical Review of England and Wales for the Year 1953*. H.M.S.O., London.
Snijders, E. P., and Straub, M. (1924). *Transactions 5th Biennial Congress, 1923, of the Far Eastern Association of Tropical Medicine*, p. 779. London.
Stocks, P. (1936). *Ann. Rep. Brit. Emp. Cancer Campgn.*, **13**, 239.
—— (1953). *Brit. J. Cancer*, **7**, 407.
Talmud, the Babylonian. Niddah. Translated by I. W. Slotki and others. Soncino Press, London, 1948.
Walker, J. M. (1949). *Quart. J. Med.*, **18**, 51.
Wynder, E. L. (1955). *British Medical Journal*, **1**, 743.
—— Cornfield, J., Schroff, P. D., and Doraiswami, K. R. (1954). *Amer. Obstet. Gynec.*, **68**, 1016.

SMOKING AND CHEWING OF TOBACCO IN RELATION TO CANCER OF THE UPPER ALIMENTARY TRACT

BY

L. D. SANGHVI, Ph.D.

K. C. M. RAO, M.Sc.

AND

V. R. KHANOLKAR, M.D.

Indian Cancer Research Centre, Parel, Bombay, 12

There is accumulating reliable and well-sifted evidence to suggest that the tendency for cancer generally to grow in man is about the same in most parts of the world. On the other hand, the "organ distribution" of cancer is often strikingly dissimilar in different groups of population, varies greatly from one country to another, and differs in different communities in the same geographical region. Thus, for instance, an earlier study (Khanolkar, 1950) showed that intraoral cancer was relatively more prevalent in Bombay than in New York or London. It accounted for 35.9% of all cancer cases at the Tata Memorial Hospital, Bombay, as against 16% of cancer cases in the New York and 6.7% in London hospitals. Further, even as regards the commonest site for the occurrence of oral cancer there is a noticeable difference in various localities in India. Cancer of the lip is the commonest type of oral cancer in Bihar, of the buccal mucosa and alveolar margin in Travancore and some parts of Madras, of the base of the tongue in Bombay, of the oral surface of the palate in Andhra, and of the hypopharynx in Assam. In Bombay, cancer of the inner lining of the cheek was four times more common among Deccani (Marathi-speaking) Hindus than among Gujarati Hindus, though their total attendance at the hospital was in the ratio of 3 : 2. Cancer of the base of the tongue and tonsils was more than twice as common among Gujaratis than among Deccanis, and more than 9 out of 10 cases occurred in men, although the male to female ratio of attendance of Gujaratis was roughly 3 : 1.

A study of these relative differences revealed several facts of considerable interest, particularly as the communities under investigation showed notable differences in habits, customs, occupations, and nutritional status. It was therefore felt that a detailed analysis of such data may yield valuable information. It may also help in assessing the contributory role of hereditary and environmental factors in the production of cancer in man.

During recent years a large number of studies have demonstrated that there is an association between lung cancer and the amount of tobacco smoked (Doll and Hill, 1950, 1952, 1954; Levin *et al.*, 1950; Mills and Porter, 1950; Schrek *et al.*, 1950; Wynder and Graham, 1950; McConnell *et al.*, 1952; Koulumies, 1953; Sadowsky *et al.*, 1953; Wynder and Cornfield, 1953; Breslow *et al.*, 1954; Watson and Conte, 1954). So far as mouth cancer was concerned, it became evident that the habit of smoking and chewing tobacco, with or without other ingredients, called for a special investigation.

The Investigation

In Western India the chewing of betel nut, betel leaf, and tobacco, and the smoking of locally prepared cigarettes ("bidis") are common habits.* It was therefore decided to collect and analyse the information available in this respect in the records of the Tata Memorial Hospital. The routine form to be filled up for every patient who is registered in the hospital contains under the head "Personal History" an item "Habits (alcohol, tobacco, etc.)." In 1952 an analysis was carried out of the information collected in this column of the cases registered during the period 1941–9. The information was scanty in the case sheets of patients with cancer other than intraoral, and those suffering from non-neoplastic conditions. This circumstance did not permit a comparison of oral cancer cases with a control group. Even in intraoral cancer, information concerning these habits was not available in as many as 19.1% of cases. Nevertheless, an analysis of the available information on the habits of patients with intraoral cancer at three different sites—namely, (1) buccal mucosa, (2) anterior third of the tongue, and (3) base of the tongue—seemed to indicate that the habit of chewing tobacco was more common in persons with cancer of the buccal mucosa and that the habit of smoking was more common among cases of cancer of the base of the tongue.

These tentative inferences obviously suggested that a systematic investigation of the chewing and smoking habits of patients with cancer of the upper alimentary tract, if it was carried out along with a corresponding control series of "no cancer" and "other cancer," was worth while. A detailed questionary was therefore drawn up and filled in for 1,460 new patients who attended the clinic during the years 1952–4. The present paper deals with an analysis of the data collected for the purpose of this investigation.

TABLE I.—*Data on the Habits of Smoking and Chewing of Tobacco in Relation to Cancer of the Upper Alimentary Tract*

	Men					Women				
	Smoking and Chewing	Smoking Only	Chewing Only	No Habit	Total	Smoking and Chewing	Smoking Only	Chewing Only	No Habit	Total
Control: Non-cancer ..	69 (24·0%)	144 (50·0%)	25 (8·7%)	50 (17·3%)	288	—	7 (6·3%)	26 (23·2%)	79 (70·5%)	112
I: Buccal mucosa	42 (44·2%)	18 (18·9%)	28 (29·5%)	7 (7·4%)	95	—	—	19	5	24
II: Oral cavity (excl. group I)	58 (40·9%)	57 (40·1%)	23 (16·2%)	4 (2·8%)	142	1	2	19	6	28
III: Oesophagus	29 (39·7%)	33 (45·2%)	7 (9·6%)	4 (5·5%)	73	2	4	9	14	29
IV: Hypopharynx	56 (38·9%)	73 (50·7%)	11 (7·6%)	4 (2·8%)	144	1	1	4	2	8
V: Base of tongue ..	73 (38·2%)	105 (55·0%)	11 (5·8%)	2 (1·0%)	191	1	1	6	4	12
VI: Oropharynx	26 (30·6%)	54 (63·5%)	4 (4·7%)	1 (1·2%)	85	—	1	4	4	9
I–VI: Total	284 (38·9%)	340 (46·6%)	84 (11·5%)	22 (3·0%)	730	5 (4·5%)	9 (8·2%)	61 (55·5%)	35 (31·8%)	110
Misc.: Other cancer ..	28 (26·2%)	49 (45·8%)	14 (13·1%)	16 (14·9%)	107	3 (2·7%)	4 (3·5%)	24 (21·2%)	82 (72·6%)	113

*A short note on the substances used for chewing and smoking in Western India is given in the Appendix.

Data

Table I contains the data on smoking and chewing of tobacco. Patients who were referred to the cancer clinic for a "check-up" and who showed no evidence of neoplastic disease were taken as the "control group." Cases of cancer of the upper alimentary canal in men were numerous enough for further analysis. There was a sufficient number of cases of cancer of the buccal mucosa to treat these as a single group (Group I). The rest of the cases of oral cancer (Group II) included: cancer of anterior tongue, 56; cancer of alveolus, 39; cancer of palate, 37; cancer of lip, 6; and cancer of floor of mouth, 4. Group VI (cancer of oropharynx) included 54 cases of cancer of the tonsil. Further analysis was not possible for women, owing to the small number of cases. The "other cancer" group consisted of cancer at sites other than the upper alimentary canal, and cancer of the breast and cervix uteri predominated in women.

The data in Table I are graphically presented in Fig. 1, which shows the percentages of smoking and chewing of tobacco in cancer cases. In Fig. 2 the percentages of men addicted to smoking and chewing are added to those accustomed to smoking only, so as to obtain the total percentages of "all smokers." Similarly, those smoking and chewing are added to persons accustomed to chewing tobacco to give the percentage of "all chewers."

The figures show that for both men and women the "non-cancer" group is similar to the "other cancer" group in smoking and chewing habits. Women with cancer of the upper alimentary tract show a higher incidence of smoking and about two and a half times the incidence of chewing compared with the control group. In men the results are more striking. It is possible to see several gradients in the incidence of habits among the different types of cancer. The proportion of men with "smoking and chewing" habits is higher in all the six groups compared with the control group, showing a diminishing proportion from group I to group VI. Similar gradients are also seen with "no habit" and the habit of "chewing only"; whereas a reverse gradient is seen with the habit of "smoking only." Fig. 2 shows the gradients of smoking and chewing separately for groups I to VI and for the control group.

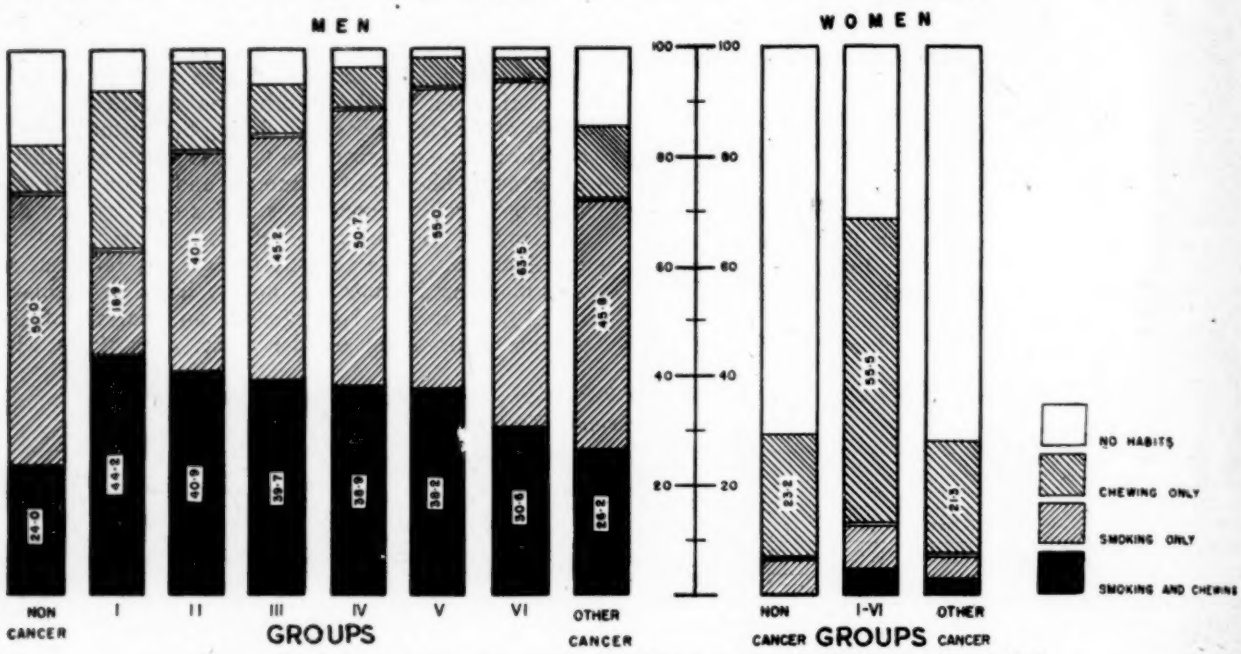


FIG. 1.—Analysis of cases of cancer of upper alimentary tract in relation to tobacco habit.

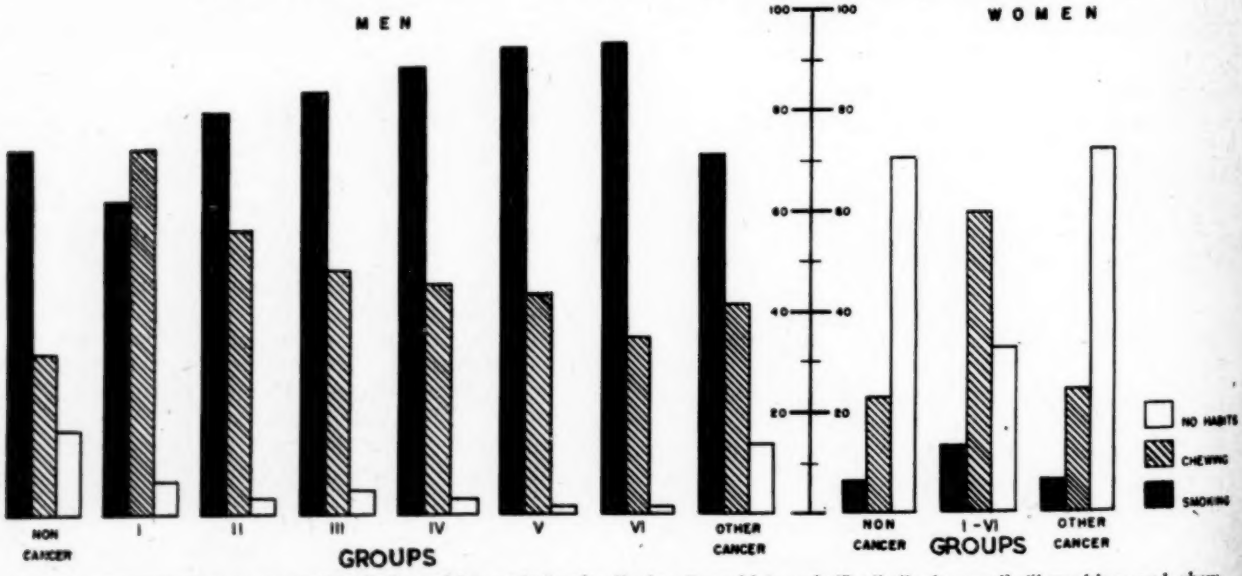


FIG. 2.—Percentage of "all smokers" ("smoking and chewing" plus "smoking only"), "all chewers" ("smoking and chewing" plus "smoking only"), and of those with no habits.

Statistical Analysis

It was necessary to take into account four variables—community, age, occupation, and sex—for purposes of evaluating the statistical significance of the smoking and chewing of tobacco in relation to cancer of the upper alimentary tract. As the two sexes presented very different patterns in habits, they were treated separately. No further analysis was carried out on the data on women owing to the small number of cases. For men, the data concerning community and age could be broken down into well-defined classes. Table II shows the differences in the smoking and chewing habits in the "non-cancer" group with respect to these two variables.

TABLE II.—*Percentage of Smokers and Chewers Among Non-cancer Men Classified According to Community and Age*

	Smoking and Chewing	Smoking Only	Chewing Only	No Habit	No. of Persons
Community:					
Hindu Deccani	31·9	39·8	12·4	15·9	113
,, Gujarati	9·2	70·4	—	20·4	54
Muslim ..	27·3	43·6	10·9	18·2	55
Other ..	19·7	56·0	7·6	16·7	66
Age:					
Less than 50	21·7	50·2	10·2	17·9	207
50 to 60 ..	30·9	45·5	5·4	18·2	55
More than 60	26·9	57·7	3·9	11·5	26

An attempt to subdivide data dealing with occupation in different classes turned out to be unprofitable. It was necessary to introduce so many groupings that finally it was difficult to justify them. Moreover, an analysis carried out on such groupings did not change the significance pattern of the types under consideration.

Dr. C. A. B. Smith, of the Galton Laboratory, London, suggested a method of analysis suitable for the present purpose. The method in essence consisted in breaking down the cancer and control cases into a number of cells for which it could reasonably be assumed that the internal variability had been substantially reduced and studying the difference and its variance for each cell. Such differences and variances could then be weighted and added to give the significance for the whole group.

Consider the following cell:

r	With Habit	Without Habit	Total
Cancer cases ..	a_r	b_r	a_r+b_r
Control ,, ..	c_r	d_r	c_r+d_r
Total ..	a_r+c_r	b_r+d_r	$a_r+b_r+c_r+d_r=n_r$

$$\text{Difference } D_r = \frac{a_r}{a_r+b_r} - \frac{c_r}{c_r+d_r}$$

$$\text{Variance of difference } D_r = \frac{(a_r+c_r)(b_r+d_r)}{(a_r+b_r)(c_r+d_r)(n_r-1)}$$

This variance is calculated on the basis of the exact distribution, keeping the marginal totals fixed.

The weighted combination of differences $D=\Sigma W_r D_r$, summed over all the cells, accordingly has the variance $V=\Sigma W_r^2 \text{ var } D_r$.

The weights W_r can be chosen arbitrarily, provided that, of course, they are decided upon previously and not influenced by the observed experimental results. Since the larger cells will give more reliable information than the smaller ones, it seems reasonable to take the weight W_r to be proportional to the total number n of observations in the cell. That is, we can take $W_r=\frac{n_r}{N}$, where $N=\Sigma n_r$.

It is obvious that the method will fail if there are no cases, either cancer or control, in any particular cell. This limitation made it necessary to restrict the analysis to three age groups—namely, under 50, 50 to 60, and over 60. Table III gives the weighted differences, and their standard errors.

This analysis shows that the habit of chewing is associated with cancer of the oral cavity (groups I and II). It shows that the combined habit of smoking and chewing is associated with cancer of the hypopharynx (group IV) and of the base of the tongue (group V). Finally, only smoking is associated with cancer of the oropharynx (group VI) and of the oesophagus (group III). There is no significant difference in smoking and chewing habits in patients with other cancers compared with the "non-cancer" group.

It was possible to make a further analysis of the smoking habit. Of the persons who smoked, 88.7% smoked bidis. During the course of the investigation, information was collected about the number of cigarettes (bidis) smoked by the patients. This information must admittedly be approximate because, even if the exact number smoked could be ascertained, there is bound to be a variability in the length of the bidis smoked by different persons. Table IV gives the average number of bidis smoked by the men in the various groups.

TABLE IV.—*Number of Bidis Smoked Daily by Patients (Men) With Different Types of Cancer of the Upper Alimentary Tract*

Control group.	Non-cancer	14·1±0·6
Group I.	Buccal mucosa	12·5±1·1
,, II.	Oral cavity (excluding group I) ..	14·6±0·8
,, III.	Oesophagus	15·3±1·2
,, IV.	Hypopharynx	16·9±0·8
,, V.	Base of tongue	17·4±0·7
,, VI.	Oropharynx	18·5±1·0

It is interesting to note that the percentage of smokers and the average number of bidis smoked show a similar trend in groups I to VI. It was not possible to carry out a further analysis of the chewing habit, as the quantities reported were often unreliable. Information regarding the duration of smoking and chewing was also unreliable.

Discussion

Experimental work on cancer has made it clear that to resort to a single or a simple explanation for the aetiology of cancer, however tempting it may be, is likely to result in failure. The contributory factors may be broadly grouped as hereditary and environmental. Such a classification is probably arbitrary, but it satisfies the needs of the present discussion.

The present study indicates that tobacco may be one of the environmental factors responsible for a large number of cases of cancer of the upper alimentary tract seen at the Tata Memorial Hospital. These populations differ sharply from other populations in their habits of tobacco chewing. The habit of chewing tobacco and the associated types of cancer lead to an assumption of the existence of a sub-

TABLE III.—*Statistical Significance of the Differences in Smoking and Chewing Habits in Patients (Men) with Different Types of Cancer Compared with the "Non-cancer" Group*

Group	Smoking and Chewing	Smoking Only	Chewing Only	No Habit	Total Smokers	Total Chewers
I: Buccal mucosa	0·133±0·057*	−0·233±0·071†	0·175±0·040†	−0·075±0·058	−0·100±0·066	0·308±0·061†
II: Oral cavity (excl. group I) ..	0·200±0·048†	−0·157±0·051†	0·100±0·034†	−0·143±0·036†	0·043±0·046	0·300±0·050†
III: Oesophagus	0·137±0·066*	0·017±0·076	−0·014±0·041	−0·140±0·055*	0·154±0·065*	0·123±0·070
IV: Hypopharynx	0·160±0·046†	−0·021±0·052	0·000±0·030	−0·139±0·036†	0·139±0·044†	0·160±0·049†
V: Base of tongue	0·200±0·046†	−0·040±0·049	−0·005±0·027	−0·155±0·032†	0·160±0·040†	0·195±0·048†
VI: Oropharynx	0·109±0·062	0·083±0·070	−0·030±0·041	−0·162±0·050†	0·192±0·061†	0·079±0·067
Misc.: Other cancer	−0·023±0·051	−0·006±0·059	0·051±0·036	−0·022±0·046	−0·029±0·054	0·028±0·055

* Shows significance at 5% level. † Shows significance at 1% level.

stance or substances in tobacco which may initiate or promote the production of cancer at the sites of prolonged contact.

The marked differences in the chewing and smoking habits among the Deccanis and the Gujaratis partly explain the differences in the incidence of cancer of the buccal mucosa and of the base of the tongue in these two communities. They also presumably explain the striking difference in the incidence of base of tongue cancer in the two sexes.

It is, however, not possible to explain all the differences on the basis of the habit of smoking and chewing of tobacco, as in all the types of cancer of the upper alimentary tract there were some persons who did not smoke or chew tobacco at all. Therefore it is necessary to explore other environmental and hereditary factors.

Sanghvi and Khanolkar (1949) encountered striking differences in the distribution of seven genetical characters among the six endogamous groups in Bombay. Data were obtained on the ABO, A_1A_2, MN, P, and Rh blood groups, taste reactions to phenylthiocarbamide, and colour vision. One endogamous group belonged to the Gujarati Hindu community, and the rest to the Deccani Hindu community. No information is available about the association of susceptibility to cancer of the upper alimentary tract with genes responsible for the above characters. It may, however, be suggested that similar differences exist for many of those genes responsible for susceptibility to cancer among different communities in India as well as in the rest of the world.

Strong and Sanghvi (1951), as a result of their study on the effects of selection on chemically induced tumours in mice, suggested tentatively that the control of tissue susceptibility to cancer might be at a different level in the mechanism of heredity than total susceptibility to cancer. They found that in mice, by selecting breeders with a longer and longer latent period (time between the injection of carcinogen and development of tumour), large variations could be brought about in the sites at which the two sexes of mice developed tumours during the course of 16 generations, without affecting to any appreciable extent the total incidence of cancer. The net result of the experiment was to increase considerably the latent period and hence the life-span of the mice which developed tumours. The mice therefore developed tumours at the sites which took an increasingly longer time interval to develop them. Such differences in the tissue susceptibility may offer one of the reasons for the habit of smoking affecting the mucosa of the upper alimentary tract in one population and the lung in another. There exists a possibility that the physical state and internal dispersal of smoke particles from bidis might differ from those of ordinary cigarettes.

Summary

The 1,460 patients who attended the cancer clinic during 1952–4 were questioned regarding the habit of smoking and chewing of tobacco in relation to cancers of the upper alimentary tract. Results of the statistical analysis showed that the habit of chewing was associated with cancer of the oral cavity; that the combined habit of smoking and chewing was associated with cancer of the hypopharynx and base of the tongue; and that only smoking was associated with cancer of the oropharynx and oesophagus. These findings are discussed.

APPENDIX

The Indian form of cigarette is known as bidi, a smoke for the common man in the country. It is made by rolling with the fingers 0.25 to 0.5 g. of tobacco flakes in a rectangular piece of dried leaf of temburni (*Diospyros melanoxylon*). Leaves of other genera and species such as *Bauhinia racemosa, Bauhinia vahlii, Butea frondosa,* and *Castanopsis indica* are also used for wrapping the tobacco. Out of about 50 known species of tobacco, only two are grown in India—namely, *Nicotiana tabacum* and *Nicotiana rustica*. Both types are used for making bidi, as well as for chewing. The tobacco is usually sun dried and cured. Bidis vary in length from 5 to 8 cm. (Fig. 3). They are conical in shape, with the tucked end (the end which is lighted) broader than the end which is held between the incisor teeth. This end is tied with a thread and flattened by pressing.

FIG. 3.—Indian cigarette (*bidi*).

In Western India the common ingredients used for chewing are betel nut, betel leaf, and tobacco. The betel nut is the fruit of the areca or betel palm (*Areca catechu*). The betel leaf is the leaf of the betel vine (*Piper betle*). Cracked or powdered dried betel nut, or slices, may be chewed alone along with a preparation of betel leaf, known as pān. Pān is prepared by applying slaked stone or shell lime and catechu to a betel leaf, and wrapping it around pieces of betel nut, with spices like the cardamom, cloves, aniseed, and several others. Catechu is an extract obtained from the wood of two species of acacia (*Acacia catechu* and *A. suma*). In Gujarat, plain tobacco is sometimes added in the preparation of a pān, whereas in the Deccan the dried and cured tobacco is commonly chewed along with betel nut and lime.

The active co-operation of our clinical colleagues at the Tata Memorial Hospital, particularly Drs. J. C. Paymaster and P. D. Schroff, made it possible for us to collect the data which have been analysed above. We should like to record our gratitude to our colleagues and to Dr. C. A. B. Smith, of the Galton Laboratory, London, for his suggestion of an appropriate statistical method.

REFERENCES

Breslow, L., Hoaglin, LeM., Rasmussen, G., and Abrams, H. K. (1954). *Amer. J. Publ. Hlth*, **44**, 171.
Doll, R., and Hill, A. B. (1950). *British Medical Journal*, **2**, 739.
—— —— (1952). Ibid., **2**, 1271.
—— —— (1954). Ibid., **1**, 1451.
Khanolkar, V. R. (1950). *Acta Un. int. Cancr.*, **6**, 881.
Koulumies, M. (1953). *Acta radiol. (Stockh.)*, **39**, 255.
Levin, M. L., Goldstein, H., and Gerhardt, P. R. (1950). *J. Amer. med. Ass.*, **143**, 336.
McConnell, R. B., Gordon, K. C. T., and Jones, T. (1952). *Lancet*, **2**, 651.
Mills, C. A., and Porter, M. M., (1950). *Cancer Res.*, **10**, 539.
Sadowsky, D. A., Gilliam, A. G., and Cornfield, J. (1953). *J. nat. Cancer Inst.*, **13**, 1237.
Sanghvi, L. D., and Khanolkar, V. R. (1949). *Ann. Eugen. (Camb.)*, **15**, 52.
Schrek, R., Baker, L. A., Ballard, G. P., and Dolgoff, S. (1950). *Cancer Res.*, **10**, 49.
Strong, L. C., and Sanghvi, L. D. (1951). *Z. Krebsforsch.*, **58**, 1.
Watson, W. L., and Conte, A. J. (1954). *Cancer*, **7**, 245.
Wynder, E. L., and Cornfield, J. (1953). *New Engl. J. Med.*, **248**, 641.
—— and Graham, E. A. (1950). *J. Amer. med. Ass.*, **143**, 329.

Mr. KENNETH PICKTHORN speaking on April 26 in a Parliamentary debate on education: "Everyone goes on repeating the stuff about science getting more and more specialized, technicalized, departmentalized, compartmentalized, and my impression, not as a scientist but as a man who has spent his life partly in intimate conversations with many of the greatest and best-informed scientists, is that the opposite has been the fact for some considerable time: the sciences have all tended more and more, during the last 20 years especially, to approximate to mathematics, and to need mathematics for any understanding of them. In that sense they have come together again."

CIGARETTE SMOKING AND BRONCHIAL CARCINOMA

EFFECT OF THE ASSOCIATION UPON SMOKING HABITS OF A GROUP OF DOCTORS

BY

D. A. PYKE, M.B., M.R.C.P.

Senior Medical Registrar, Radcliffe Infirmary, Oxford

Doll and Bradford Hill (1950) demonstrated a significantly higher incidence of carcinoma of the bronchus among those who smoked cigarettes than among those who did not. This finding has been confirmed and amplified here and in America, and public endorsement has been given by the Minister of Health and the Secretary of the Medical Research Council.

What effects have these statements had? Do people now smoke less?

In an attempt to answer these questions a small inquiry has been made of 217 doctors. It was thought that doctors would be sensitive to scientific argument and might be among the first to reduce their smoking in the face of evidence of its danger; they are more likely to be familiar with the facts making up this evidence and with the character of the disease.

Material and Methods

All the 217 doctors working in the hospitals in Oxford were sent a short questionary. Nine-tenths of them were men; their ages ranged from about 24 to 65, about two-thirds were under 40.

DO YOU SMOKE CIGARETTES?

If "*Yes*," for how many years have you smoked?

Do any of these statements represent your views?

(i) I am not satisfied with the evidence linking cigarette smoking with carcinoma of the bronchus.

(ii) I am satisfied with the evidence and hope to give up smoking, but have not yet been able to bring myself to do so.

(iii) I am satisfied with the evidence but do not intend to give up smoking.

(iv) Other.

If "*No*," have you ever smoked (by which is meant at least one cigarette a day for a year or more)?

If you have once smoked but have given it up, can you give the date (as precise as possible) of stopping?

What was your reason for stopping?

Non-smokers were also asked to say whether they were satisfied or not with the evidence linking smoking with carcinoma of the bronchus.

Pipe and cigar smoking was not considered, nor was the number of cigarettes smoked. Figures of the national consumption of cigarette tobacco and of the number of smokers in the country were also obtained.

Results

Replies were received from 211 (97%) doctors. Less than half of them smoked cigarettes. About a quarter had discontinued the practice, and another quarter had never smoked (Table I).

TABLE I

	211 Doctors	General Population (U.K.)*
Smoke now	47·4% (100)	57% (men 72%, women 42%)
Once smoked	25·1% (53)	43% („ 28%, „ 58%)
Never „	27·5% (58)	

* Figures calculated from the Hulton Readership Survey and the 1% sample of the 1951 census.

Changes in the Number of Smokers

Smoking Begun.—In the last eight years 11 of the 211 doctors have started to smoke cigarettes. Five began to do so eight years ago, one seven years ago, two six years ago, one five years ago, one four years ago, one two years ago.

Smoking Stopped.—In the last eight years 40 of the doctors have stopped smoking. The dates of stopping were: Before September, 1946, 13; September–December, 1946, 1; 1947, 6; 1948, 6; 1949, 2; January–September, 1950, 3; October–December, 1950, 2; 1951, 3; 1952, 3; 1953, 5; 1954, 9. In the four years immediately before the publication of Doll and Bradford Hill's first paper (September, 1946, to September, 1950), 18 persons stopped smoking. In the next four years, ending at the time of the survey (October, 1954), the number was 22.

Reasons for Stopping Smoking.—The 53 members of this group gave 63 reasons for having stopped smoking (Table II).

TABLE II

Minor ill-health (e.g., cough, sore throat)	15
Expense	13
Lack of desire	8
Risk of carcinoma	8
After or during an illness	6
Unclassified	13

The 13 doctors giving expense as a main reason had stopped smoking in 1947 (2), 1948 (1), 1950 (2), 1951 (1), 1952 (2), 1953 (1), 1954 (4).

National Figures.—The decline in the number of smokers among this group of doctors is not reflected in the national figures (Table III).

TABLE III.—*Number of Cigarette Smokers and Their Weekly Consumption per Head (United Kingdom)**

	No. of Cigarette Smokers (Millions)			Average No. of Cigarettes Consumed Weekly per Cigarette Smoker		
	Males	Females	Total	Males	Females	Total
1947	11·7	8·4	20·1	113	49	97·9
1948	11·8	7·8	19·6	105	42	79·9
1949	11·8	7·6	19·4	99·4	45·5	78·3
1950	11·9	7·3	19·2	100·1	45·5	79·3
1951	11·8	7·3	19·1			
1952	11·4	7·5	18·9	105	46·9	81·9
1953	11·2	7·5	18·7	100·8	49·7	80·3
1954	11·4	7·9	19·3	102·9	51·1	81·7

* Based on the Hulton Readership Survey. Figures are not available for the years before 1947 and only abbreviated ones for the year 1951.

The fall in the number of cigarettes smoked, but only slightly in the number of smokers, between 1947 and 1948 may have been due to the large tax increase in the budget of 1947. Since then, and during the time when an association between smoking and carcinoma has been known, there has been very little change. Figures of the total cigarette tobacco consumption (in lb. per annum per head of the population of the United Kingdom)† show the same steadiness in recent years (Table IV).

TABLE IV

1946	1947	1948	1949	1950	1951	1952	1953	1954
4·6	4·0	3·7	3·6	3·6	3·8	3·8	3·9	4·0

Opinion of the Evidence Linking Smoking and Bronchial Carcinoma

Opinions of the validity of this evidence were given by 193 doctors. Rather more than half were satisfied with the evidence of an association between smoking and carcinoma of the bronchus, but the figures differ considerably among the smokers, non-smokers, and former smokers (Table V).

If the 193 are divided into (1) present and past smokers and (2) non-smokers, and their opinions examined separately it is seen that in group (1) 76 were satisfied and 57

†Based on estimates provided by the Board of Trade.

TABLE V

Opinion of the Evidence	Smokers	Former Smokers	Non-smokers	Total
Satisfied	46	30	34	110 (56·5%)
Not satisfied ..	45	12	5	62 (32·5%)
Undecided ..	9	3	9	21 (11·0%)

unsatisfied with the evidence, a ratio of 1.3 to 1. In group (2) the figures are 34 and 5, a ratio of 6.8 to 1 in favour of accepting the evidence. Thus, excluding those who were undecided, over five times as many non-smokers as present and former smokers accepted the evidence.

Of the 46 smokers who do accept the evidence 14 hope to discontinue smoking and 32 do not intend doing so.

Discussion and Conclusions

Less than half of this small group of doctors smoke cigarettes, a lower proportion than among the general population. The proportion of those who have never smoked (27.6%) corresponds closely to Doll and Bradford Hill's (1954) finding of 28.5% of non-cigarette smokers among male doctors aged 35–44.

In the present group of 211 doctors the number who smoke cigarettes is gradually declining. Eight years ago it was 129, now it is 100.

To judge from the reasons which those who have discontinued smoking give for doing so and from figures of national tobacco consumption it appears that increased cost is a considerable factor in reducing cigarette smoking, but that the risk of cancer is not (although it may be a deterrent to starting the habit). This is supported by the fact that the number of doctors giving up smoking since an association with bronchial carcinoma was discovered has not increased. It seems, therefore, that further demonstration of this association will not lead to many more doctors stopping smoking.

The proportion of those who accept the evidence of an association between smoking and carcinoma of the bronchus is so much higher among the non-smokers than among the smokers, present and past, that personal prejudice may have played some part in shaping these opinions. Possibly the pleasures of tobacco addiction persuaded some of the smokers to discount the evidence of its dangers.

Summary

The 217 doctors working in the hospitals of Oxford were questioned about their cigarette-smoking habits, and 211 (97%) replied: 47.4% smoke cigarettes, 25.1% once smoked, and 27.5% have never done so. The proportion who smoke is gradually declining, but the number of doctors giving up smoking has not increased since the discovery of an association between smoking and carcinoma of the bronchus. Figures for national tobacco consumption and number of smokers have shown no decline since 1950, when Doll and Bradford Hill's first paper appeared.

Only a little over half (56.5%) of the doctors were satisfied with the evidence linking carcinoma of the bronchus and smoking; but the proportion was more than five times higher among the non-smokers than among the smokers. Perhaps the smokers were persuaded by their fondness for tobacco to discount unpalatable evidence.

I am most grateful to the 211 doctors for their co-operation and to Dr. A. M. Cooke for his criticisms.

REFERENCES

Doll, R., and Hill, A. Bradford (1950). *British Medical Journal*, **2**, 739.
—— —— (1954). Ibid., **1**, 1451.

PHYSIOLOGICAL PRINCIPLES IN THE TREATMENT OF THE UNCONSCIOUS PATIENT*

BY

WILLIAM W. MUSHIN, M.A., M.B. F.F.A. R.C.S., D.A.

Professor of Anaesthetics, Welsh National School of Medicine, Cardiff

The title of this paper crystallizes the main concern of the anaesthetist so far as the administration of general anaesthesia is concerned. He deliberately administers combinations of powerful drugs to produce unconsciousness of varying depth. His skill lies not only in the administration of these drugs, but in the treatment of the resulting unconscious state. The essential problems attendant on unconsciousness *per se* are the same whatever the cause, be it anaesthesia or head injury or barbiturate overdose. There therefore seems to be some justification for extending the discussion beyond the confines of anaesthesia to include unconsciousness in general. As for the physiological principles which underlie the treatment of the unconscious state, the need for them here is no less than in the treatment of other pathological states—indeed more, since a disregard of such principles so easily leads to permanent damage or death.

What is Unconsciousness?

"Unconsciousness" is a term applied to three separate states which have much in common with each other and yet differ fundamentally in their aetiology and prognosis. They are natural sleep, anaesthesia, and coma. In each of these the patient loses his power of perception of the world in which he lives, and on recovery has no memory of events which took place during that time. Though he may respond in a reflex manner to stimuli, such reflex activity leaves no trace in his conscious memory. Natural sleep is distinguished by the fact that it occurs in the absence of disease or the administration of drugs. It terminates spontaneously after a varying interval, but in any case is easily interrupted by the application of external stimuli of very moderate intensity. Anaesthesia differs from coma only in the fact that it is to a great extent reversible and controllable by the anaesthetist. It is the result of the deliberate administration of drugs or of physical agencies such as cold or electrical currents. The term "coma" is best reserved for states of unconsciousness associated with disease, injury, or overdose with certain drugs. It may on occasion be reversible, but it is generally not controllable. The two differ little so far as the physical state of the patient is concerned, and it would be generally impossible on clinical examination alone, and without knowing the circumstances, to say whether the state is one of anaesthesia or of coma.

The depth of unconsciousness may vary widely from patient to patient, and is determined by the individual ability to respond to stimuli of varying intensity. When a patient responds reflexly to mild painful stimuli his unconsciousness is said to be light, but in profound unconsciousness it may be that no stimulus of any kind produces a response and only a beating heart and active respiration show that the patient is still alive.

*Based on a lecture given before the Royal Faculty of Physicians and Surgeons of Glasgow on January 19, 1955.

Why Treatment is Needed

It might appear that the unconscious patient needs no treatment apart from the removal of the causes of his unconsciousness, whereupon he would return to consciousness and recover. This is certainly true in a number of instances, but there is a great risk that in the absence of positive treatment certain complications may arise which may be fatal or leave permanent effects.

Respiratory Depression

The very state of unconsciousness is outward evidence of a depressed activity of the cerebral cortex. Concomitant with this there is always depression of the rest of the brain, including the medullary centres. Respiration is therefore also depressed. Even more important than the reduction in the total minute volume of respiration is the reduction in tidal volume. When the size of the latter approaches that of the physiological dead space, hypoxia is present in some degree and the patient becomes cyanosed. This is because, in these circumstances, at each breath exchange of air takes place only between the dead space and the outer air. A good example of this is the patient who has tachypnoea due to an overdose of trichlorethylene. The respiratory rate may be 40–50 per minute, but, since at each breath no more than perhaps 200 ml. of air is inhaled, cyanosis is present, even though the minute volume of respiration is high—10 litres or more per minute. Another example is the depression that occurs after overdosage with morphine or a barbiturate drug. Not only is the respiratory rate slowed, but the breathing is very shallow. When the volume of each inspiration is reduced to 150–200 ml. the patient usually becomes cyanosed. This explains why there is a limit to the slowing of respiration before death supervenes. Even were the patient taking good-sized breaths of 500 ml., at least three or four of them every minute would be required to give him enough oxygen. It is therefore impossible for such a patient to breathe at less than, say, four times a minute and live. Periodic breathing is common in unconscious patients, and is further evidence, if such were needed, of suboxygenation of the medulla.

Respiratory Obstruction

The respiratory depression of the unconscious patient may be, and often is, complicated by obstruction of the airway, either by a relaxed tongue and pharynx or by secretions or vomit. Secretion in the respiratory tract appears very quickly in the presence of respiratory obstruction, and such fluid is not salivary in origin. In these circumstances the secretion is generally the result of some degree of what is known, for want of a better term, as pulmonary oedema. The high intrapulmonary negative pressure consequent on respiratory obstruction upsets the delicate equilibrium at the alveolar membrane which keeps fluid from entering the alveoli from the blood stream. Liquid then easily passes from the blood stream into the alveoli and thence into the respiratory tract. (See under "Complications.")

Circulatory Depression

Treatment is also needed because of the disturbances of circulation. Particularly in anaesthesia, but also in many other states, the heart muscle itself is depressed, and in any case will soon become so when hypoxia develops. The action of the heart is further hindered by the depressed breathing. The "thoracic pump" effect of breathing on the venous return of blood is lessened, the output of the heart is reduced, and the blood pressure tends to fall. At the other end of the circulatory system the capillaries are affected by hypoxia and by the accumulation of metabolic products, which quickly follow in the train of depressed breathing. Peripheral resistance is lowered and the blood pressure tends to fall still further. A vicious circle is started: poor cardiac output and low blood pressure mean poor pulmonary circulation and poorer oxygenation; the lower blood pressure ultimately means less coronary flow and still further depression of the heart muscle.

Other Effects

Metabolism is generally lowered during unconsciousness. Water loss, too, occurs continuously, and ultimately with the passage of time the problem of water balance and nutrition arises. There are certain other problems, minor if guarded against, but major in their possible ill-effects. Two examples are the possibility of the inhalation of vomit and the possible development of nerve palsies through malposture.

If untreated, therefore, the unconscious patient develops increasing hypoxia, with tissue and pulmonary oedema and circulatory failure. His metabolism is lowered and his fluid balance disturbed; secretions and vomit may be inhaled and postural palsies develop.

Treatment of the Unconscious State

The first principle of treatment of the unconscious patient, and one on which all else depends, is the maintenance of an adequate supply of oxygen to the tissues. Air or oxygen must first reach the alveoli in sufficient amount, and then enter the blood stream. I am sometimes shocked that this elementary fact is not appreciated outside the field of anaesthesia. My last experience of this was in connexion with a case labelled "cerebral malaria," to which I had been called because an oxygen regulator was out of action. The toothless patient, with a hanging lower jaw, was propped up in bed, unconscious, cyanosed, and clearly dying. Each breath was made with effort, and the sucking-in of his chest was striking. I immediately held up the patient's jaw, and to the amazement of those present the stertor disappeared, the patient became pink, and within a few hours was fully conscious. He ultimately left hospital a fit man.

If the jaw cannot be held in such a way that breathing is free for long periods of time, or if the unconsciousness is profound, an endotracheal tube should be inserted without hesitation. The insertion of a tube into the trachea should no longer be regarded as requiring unusual skill or as carrying great hazard. The manœuvre is performed daily by anaesthetists, and is a life-saving measure when the patency of the airway cannot be maintained by other means. The introduction of the practice of intubating seriously ill patients with respiratory insufficiency in spinobulbar poliomyelitis, and more recently in tetanus, has had a dramatic effect on the prognosis of these diseases. I believe that a more widespread appreciation of the importance of a perfect airway will lead to a greater use of tracheal intubation with good results. If the unconsciousness is likely to persist for more than one or two days a tracheostomy is preferable to an endotracheal tube, since trauma to the cords is avoided and the respiratory tract is more easily kept free of secretions.

Suction

An important accessory aid to a clear airway is the use of mechanical suction. There can be few hospitals without a suction apparatus, and one of these instruments must also be regarded as essential for domiciliary use. Without going too deeply into mechanical matters, I would like to point out that the "power" or "strength" of the apparatus refers to the rate at which it removes fluid. The negative pressure indicated on a manometer is by itself of little interest. A good hypodermic syringe can produce almost a vacuum, but is useless as a "sucker" because its liquid removal rate is maintained for only a brief moment. The accompanying chart gives the results of some experiments with a piped suction installation, and illustrates some further points. For the removal of vomit or secretion a mechanical sucker is unequalled. Even with an efficient sucker, and certainly in its absence, gravity can still save life. A head-down position allows vomit to fall to the floor and prevents its accumulation in the pharynx, whence it may be inhaled.

Carbon Dioxide

Even when the airway is perfectly clear hypoxia may still be present owing to shallow breathing. The administration

of oxygen helps in these cases, but until ventilation has increased and tidal exchange become larger inadequacy of oxygenation may persist. Shallow breathing is a temptation to use carbon dioxide. But poor ventilation itself results in an accumulation of carbon dioxide, and the depressant effects of this gas on the central nervous system and the myocardium are now being appreciated to a much greater degree than formerly. The carbon-dioxide content of the blood of a depressed unconscious patient is generally high,

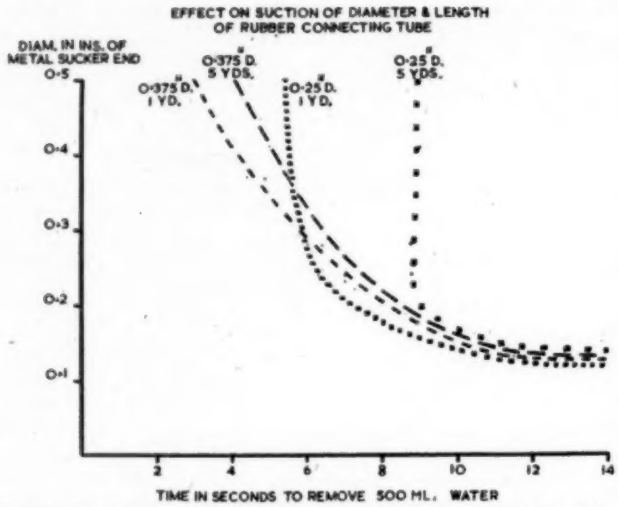


Chart showing the results of experiments with a piped suction installation. In the case of small-bore tubing, increasing the diameter of the metal sucker end has little effect in improving the fluid-removal rate. Improvement is effected by shortening the connecting tubing. The best results are obtained with large-bore connecting tubing and large-bore metal sucker end.

and more than enough to stimulate the respiratory centre if only the sensitivity of the centre is restored by an adequate supply of oxygen. Carbon dioxide from a cylinder plays little or no part in the treatment of respiratory depression. There is, indeed, a grave danger attached to its use, since a concentration above 7% has a powerful depressant effect on the central nervous system; in fact a high concentration was at one time deliberately used as an anaesthetic.

Oxygen

The average patient produces between 200 and 300 ml. of carbon dioxide per minute, and this must be expelled through the respiratory tract. At least 5 to 6 litres of other gases is required if this amount of carbon dioxide is to be diluted to 5%, the normal concentration in the alveoli. If oxygen therapy is instituted, at least 6 litres of oxygen must flow into the bag or tent. A smaller amount than this cannot possibly produce a sufficient partial-pressure differential of carbon dioxide across the alveolar membrane for the expulsion of the full amount of the gas.

Analeptics

An old-fashioned way of treating narcotic poisoning was to slap the patient's face and drag him round the room; another was to dilate the anal sphincter. The aim of these and similar methods, including the injection of analeptics, is to stimulate breathing reflexly. I cannot, however, support or encourage such methods. When a patient is deeply depressed, only oxygenation of his vital organs, particularly the brain, could keep him alive. Analeptics and physical stimuli are generally useless in such cases. Their continued administration when they fail to produce response is usually evidence of lack of appreciation of the depth of depression of the patient's central nervous system. It should be borne in mind, however, that spontaneous respiration in the presence of anoxia may be largely the result of stimulation of the carotid body by anoxia. Oxygen overcomes this, but if the respiratory centre is too depressed for carbon-dioxide stimulation to be continued apnoea may result. Such a patient may need assisted respiration until his respiratory centre recovers sufficiently from its depression.

Artificial Respiration

An excellent method of maintaining artificial ventilation of a depressed patient for long periods of time is the box or cabinet respirator. The fact that a sub-atmospheric pressure is produced round the body with this type of apparatus should not obscure the similarity between it and rhythmic positive-pressure ventilation. In both the essential feature is the creation of a differential between the pressure at the lips and that in the chest. It makes little gross difference to the respiratory or circulatory mechanics whether that differential is produced by raising the air pressure round the head or by lowering it round the body.

Of the numerous methods of artificial respiration that are still in common use, the only one suitable for emergency clinical use is inflation of the lungs. There was at one time among physicians a general suspicion of inflation of the lungs with air or oxygen at a pressure above that of the atmosphere, on the ground that such a pressure may injure the alveoli. It should be remembered in this connexion that when the procedure is carried out with a thin rubber bag the maximum pressure attainable is of the order of 30–40 cm. of water. This is far below the intrapulmonary pressure of over 100 cm. of water which can be voluntarily generated by closing the larynx and forcefully expiring. It is likely that a pressure much in excess of 150 cm. of water is required before alveolar damage occurs. None of the foregoing would, of course, exclude the risk of rupturing an unsuspected subpleural bulla, but this risk is present in everyday life quite apart from artificial respiration. There are, however, certain disadvantages of positive-pressure inflation of the lungs which should be known, though they are generally insignificant as compared to the advantages. There is, first, a possibility of occluding the alveolar vessels at the peak of each inflation. To avoid this the mean inflation pressure should be as low as possible, with peaks not in excess of 15–20 cm. of water, and even this pressure should not be maintained for more than a fraction of the cycle. A sharp peak to the pressure curve rather than a plateau is the objective. The other risk is that too vigorous, and particularly too frequent, a rhythm of positive pressure may so tamponade the heart and impede the normal return of venous blood by the thoracic pump that the cardiac output is impaired. Prophylaxis here consists in applying a slow rhythm and allowing a rapid return of the intrapulmonary pressure to that of the atmosphere at the end of each inflation. These measures ensure that the mean intrapulmonary pressure is low and the circulatory impedance as low as possible.

Posture

The common practice of placing an unconscious patient flat on his back exposes him to the hazards of respiratory obstruction and of inhaling vomit and secretions. A better posture, and one which to a large extent overcomes these risks, is to place him on his side. Vomit and secretions collect in the cheek and, if there is a slight head-down tilt, will run out, while the flaccid tongue falls to one side and the airway does not become obstructed. At regular intervals, say once an hour, the patient should be turned to the other side to encourage good circulation on the two sides of the body to improve venous return.

Maintenance of Fluid Balance

In an unconscious patient it is essential that the fluid and electrolyte balance be maintained. Only losses should be replaced. The accurate and careful charting of fluid balance should be started at the earliest moment, regard being paid to the importance of vomit and sweating as sources of fluid loss. Nutrition becomes a problem only in unconsciousness lasting more than a couple of days; owing to the low metabolism in such cases a daily intake of about 1,500 calories is generally adequate.

Complications

Resistance to Breathing

In discussing the treatment of unconsciousness attention should be drawn to the importance of minimizing the resistance to breathing imposed by the use of such devices as endotracheal tubes and oxygen-therapy apparatus. It is essential that a patient, particularly one whose respiration is depressed, should not be required to make more effort to breathe than is necessary. If such effort is called for the patient becomes physically exhausted, and if the effort required is too great he may be incapable of making it. As a result the lungs are not filled quickly enough and oxygen intake is lowered. In addition, the intrapulmonary negative pressure at the height of inspiration may be greatly increased and the path prepared for pulmonary oedema. With an endotracheal tube, or any other gas pathway through which the patient is made to breathe, the factors which influence resistance are the diameter and length of the instrument and the presence of sharp corners—all being equally important. In any case, the use of endotracheal tubes, invaluable though it is in preventing respiratory obstruction, does not mean that further obstruction cannot occur. Kinking at the back of the pharynx and the passage of a tube into one bronchus are not infrequent and must be watched for.

Pulmonary Oedema

A common complication of the altered mechanics of respiration in the unconscious patient is pulmonary oedema. Most physicians and anaesthetists have had experience of the speed with which moist sounds, and even frothy sputum, appear in the respiratory tract of such a patient. To understand why pulmonary oedema readily appears in these circumstances it is necessary to indicate briefly the normal equilibrium across the alveolar membrane which keeps liquid within the circulatory system. This consists of a balance of forces. On the one hand there is the pressure within the alveoli, falling a little at each inspiration and returning to atmospheric pressure during expiration; on the other side of the membrane is the vascular system. A filtration force of 10 mm. Hg, the systolic pressure, tries to force fluid out into the alveoli, while the osmotic pressure of the blood proteins, of about 20–25 mm. Hg, acts in the reverse direction. When respiratory obstruction is present the intra-alveolar pressure falls unduly at each inspiration, tending to expel fluid. This is further enhanced if the patient has a right heart failure of any degree, leading to a high pulmonary arterial pressure, or has been injudiciously given blood transfusion or saline infusion. If in addition there is a general anoxia, the alveolar cells and the alveolar vessels also become anoxic, their permeability is increased, and a vicious circle created. Suction can clear fluid only from the trachea and main bronchi; it cannot empty the alveoli. Positive-pressure ventilation with an unobstructed airway can reverse this process. Confirmation of this view may be found in the growing practice nowadays of treating the respiratory depression of barbiturate overdose, the respiratory paralysis of poliomyelitis, and also the paralysis induced by curare in cases of tetanus, by means of tracheostomy, positive-pressure ventilation, and frequent suction. In these instances oxygenation is ensured, the respiratory tract kept clear, and pulmonary oedema prevented.

Summary

An outline is given of the main physiological problems common to unconscious patients whatever may be the underlying cause, and in particular those of interest to an anaesthetist.

Treatment resolves itself into ensuring adequate oxygenation by means of a clear airway, with some form of assisted or artificial respiration where indicated. The improved circulation, with fluid loss made good, combines with the improved oxygenation and respiratory mechanics to prevent the altered dynamics across the alveolar membrane which leads to pulmonary oedema and may prove fatal. Many an unconscious patient who has been adequately treated for the underlying cause dies unnecessarily because these fundamental physiological requirements are not met.

TREATMENT OF LEUKAEMIA AND ALLIED DISORDERS WITH 6-MERCAPTOPURINE

BY

JAMES R. FOUNTAIN, M.B., M.R.C.P.Ed.

Medical Tutor, Department of Medicine, the General Infirmary at Leeds

Within the past ten years a number of chemical agents which produce temporary beneficial effects in leukaemia and allied diseases have been discovered. Their introduction has usually come about in one of three ways: (*a*) the observation that a compound being investigated for other reasons has a depressant effect on haemopoietic tissues—for example, nitrogen mustard and urethane; (*b*) the synthesis of compounds related chemically to substances already known to be effective, such as in the case of triethylene melamine, triethylene phosphoramide, and naphthyl-di-2-chlorethylamine (R.48); and (*c*) the synthesis of analogues of nucleic-acid precursors. It is on the last group that so much attention is now being focused. Undoubtedly the observation by Farber *et al.* (1948) that two folic-acid conjugates, pteroyl-diglutamic acid and pteroyl-triglutamic acid when given to children with acute leukaemia resulted in an acceleration of the leukaemic process gave considerable impetus to research in this particular field. The sequel was the synthesis of the 4-amino analogues of folic acid, aminopterin and amethopterin, which were found to suppress the growth of leukaemic tissue and produce temporary remissions in some children with acute leukaemia (*Proceedings of the Second Conference on Folic Acid Antagonists*, 1952).

With the knowledge that folic acid was essential for the synthesis of nucleic acid, antagonists of other nucleic-acid precursors have been prepared and tested for antileukaemic activity. 2:6-Diaminopurine, an analogue of adenine, has been shown (Burchenal, Bendich, *et al.*, 1949; Burchenal, Johnston, *et al.*, 1949) to prolong the survival time of mice with transplanted leukaemia. Burchenal, Karnofsky, *et al.* (1951) reported remissions in five of a series of 25 patients with acute leukaemia treated with this compound. Compounds containing the 2:4-diamino-pyrimidine moiety, including those with antimalarial activity (Falco *et al.*, 1949), were shown to be competitive antagonists of folic acid in the growth of *Lactobacillus casei* (Hitchings *et al.*, 1952), and in animals states indicative of folic-acid deficiency were observed. These findings suggested that such compounds might be effective in acute leukaemia, and it has been shown (Burchenal, 1954) that one such pyrimidine analogue, 2:4-diamino-5(3′4′-dichlorphenyl)-6-methylpyrimidine, produced occasional remissions in children with this disease. Farber, Foley, *et al.* (1953) have shown that a related series of compounds, the dihydrotriazines, have the property of temporarily inhibiting the growth of the leukaemic process in children.

Of the purine and pyrimidine derivatives discovered to date, the most effective in the treatment of leukaemia is the analogue of adenine and hypoxanthine, 6-mercaptopurine (6-MP). This substance, known by the proprietary name "purinethol," has been shown by Burchenal, Murphy, *et al.* (1953) to have produced good clinical and haematological remissions in 15 out of 45 children with acute leukaemia, and in another 10 patients partial remissions and clinical improvement. The same authors described occasional remissions in adult patients with the disease, and encouraging results in patients with chronic myeloid leukaemia.

The present study is based on experience gained in the treatment of 26 patients since June, 1953. Of these, 13 had acute leukaemia, 7 chronic myeloid leukaemia, 2 chronic lymphatic leukaemia, 2 multiple myeloma, 1 mycosis fungoides, and 1 erythroderma secondary to an underlying reticulosis of undetermined type.

PLAN OF TREATMENT

Patients were unselected and none received other forms of chemotherapy previous to, or as a supplement to, treatment with 6-MP. Blood transfusions and antibiotics were prescribed as the need arose. All patients received the initial course in hospital, and clinical and haematological examinations were performed daily or on alternate days. The bone marrow was examined at intervals, generally of two weeks, in cases of acute leukaemia. Patients who improved sufficiently were later followed up in the out-patient department and had blood examinations at weekly or fortnightly intervals.

The dosage of 6-MP was based on that suggested by Burchenal, the initial dose being approximately 2.5 mg. per kg. body weight. Thus a 5-year-old child was started on 50 mg. and an adult on 150–200 mg. per day, measured to the nearest 25 mg. The same dosage scheme was used both for patients with acute and those with chronic leukaemia, and in all instances the daily amount was divided into doses of 25 or 50 mg. given over the 24-hour period.

RESULTS OF TREATMENT

A. Acute Leukaemia

The criteria for a complete remission were strict and consisted of: (*a*) disappearance of all clinical evidence of disease and return of patient to full activity; (*b*) return of peripheral blood picture to normal; and (*c*) return of bone marrow to apparent normality with disappearance of blast cells or reduction to less than 10% of total cell count. A partial remission was said to be present when clinical and haematological improvement was considerable but fell short of the criteria of a complete remission.

Of 13 patients, seven responded to treatment. Five (two children and one adult with acute lymphoblastic leukaemia, and two adults with acute myeloblastic and acute monocytic leukaemia respectively) developed a complete clinical and haematological remission lasting from seven weeks to seven months. One patient, a child aged 3½ years, relapsed after remission lasting three months, but further treatment resulted in a second remission of four months' duration. Resistance to therapy has been observed following relapse, and in only one case has 6-MP been effective a second time. One adult and one child showed temporary, partial clinical and haematological improvement, while six patients (three adults and three children) failed to respond to treatment, four dying within the first week.

Illustrative Cases

CASE 1: ACUTE LYMPHOBLASTIC LEUKAEMIA.—A boy aged 3½ years was admitted to the General Infirmary at Leeds on June 20, 1953. Five weeks previously mumps had been diagnosed, and he then got rapidly worse. He lost appetite and pain in the legs prevented him from walking. Increased pallor was noticed and the temperature was at times raised. On admission he was anaemic, and there were enlarged lymph nodes in the cervical, axillary, and inguinal regions, also numerous small scalp tumours. The skin, throat, and mouth appeared healthy; the liver and spleen were not palpable. There was no pyrexia.

Blood studies supported a diagnosis of acute lymphoblastic leukaemia. On June 26 blood findings were: Hb, 6 g. per 100 ml.; R.B.C., 1,900,000 per c.mm.; reticulocytes, 1.9%; platelets, 60,000 per c.mm.; W.B.C., 4,800 per c.mm. (blast cells 17%, lymphocytes 83%). The tibial bone marrow was highly cellular and replaced by lymphoid cells, of which 56% were primitive cells with the characteristics of lymphoblasts, while the rest were more or less mature lymphocytes. Packed red cells were immediately transfused, raising the haemoglobin level to 13.5 g. On the same day 6-MP therapy, 50 mg. by mouth daily for nine days, was started. On July 5 this was increased to 75 mg. daily for five days, and during the next two days a further 75 mg. was given. 6-MP was stopped on July 11, after a total of 0.9 g. had been given. During treatment the child's condition remained good, pain in the legs was moderate, and he was afebrile. On July 14 the lymph nodes and scalp tumours were impalpable, and the white cell count had fallen to 850 per c.mm. and the haemoglobin to 9.6 g. Leucopenia persisted for three weeks and was followed by haematological remission.

On August 1 the leucocyte count was 4,000 (polymorphs 55%, lymphocytes 45%) and the platelet count 169,000 per c.mm. Blast cells in the tibial bone marrow had decreased to 6.4%; lymphocytes were 17.2%, myeloid cells 46.4%, and erythroid cells 30.0%, and the marrow was less cellular. The presence of erythroid elements was reflected in the rising haemoglobin level and red cell count, which on August 5 were 12.2 g. per 100 ml. and 4,000,000 per c.mm. respectively.

The patient was discharged on August 11. Physical examination revealed no abnormality, his appetite was good, and he regained full activity. Full clinical and haematological remission continued for three months, when relapse occurred. He was readmitted to hospital, and a second course of treatment with 6-MP for seven weeks again led to a complete remission lasting four months, during which a daily maintenance dose of 25 mg. 6-MP was prescribed. He had now become resistant to 6-MP, and A.C.T.H. was substituted. Although he has since been persistently leukaemic, his clinical condition has been fairly good. He has now survived over a year since the disease was diagnosed.

CASE 2: MONOCYTIC LEUKAEMIA (NAEGELI TYPE).—A 44-year-old baker was admitted to St. James's Hospital, Leeds, on June 9, 1953, with a four-weeks history of lumbar pain and of sweating and dyspnoea on exertion. Examination showed widespread ecchymoses, and two small skin tumours in the xiphisternal region. Sacral oedema was present; the liver was palpable 6 cm., and the spleen 5 cm., below the costal margin. The temperature was normal; no other physical abnormalities were found. A chest radiograph was normal. Biopsy showed the skin tumours to be due to leukaemic infiltration. The blood count on June 11 was: Hb, 8.5 g.; R.B.C., 2,800,000 per c.mm.; reticulocytes, 1%; platelets, 66,000 per c.mm.; W.B.C., 6,800 per c.mm. (blast cells 11%, myelocytes 11%, neutrophils 30%, eosinophils 11%, basophils 1%, lymphocytes 22%, monocytes 14%). The sternal bone marrow showed: blast cells, 59%; myeloid cells, 12%, erythroid cells, 8.5%; lymphocytes, 15%; other cell types, 5.5%. Megakaryocytes were scanty. Many of the primitive blast cells were monocytoid, the appearance suggesting a Naegeli-type monocytic leukaemia.

Treatment with 6-MP, 100 mg. daily by mouth for seven days, was begun on June 15. On June 22 the patient had severe dyspnoea owing to a large left-sided pleural effusion, and 2 pints (1.1 litres) of haemorrhagic fluid was removed. The dose was then increased to 200 mg. daily. Whole blood was transfused on the fifth day of treatment, raising the haemoglobin level to 10.5 g. No clinical or haematological change occurred during the first three weeks of treatment. On July 8 the patient felt much better, the lumbar pain had disappeared, and his appetite improved. The size of the liver

and spleen had not changed, however, and a large pleural effusion was still present. The haemoglobin level had fallen and more whole blood was transfused. The leucocyte count was 4,200 and the platelet count 85,000 per c.mm. The leucocyte count continued to fall, and treatment was stopped on July 14, when leucocytes numbered 1,200 per c.mm.; a total dose of 5.3 g. of 6-MP had been given. He was now symptom-free: the liver was impalpable, and the lower pole of the spleen could be felt only on deep inspiration. The remaining skin tumour had disappeared, but fluid was present in the left pleural cavity and a further 2 pints was removed on July 13. On July 14 the sternal bone marrow was hypocellular and blast cells had decreased to 10%.

The platelet count three days after stopping treatment rose to 192,000 per c.mm., and thereafter remained normal. Leucopenia persisted for two weeks, the leucocyte count then rising to normal. On July 29 findings on physical examination were normal and the blood picture was as follows: Hb, 11.5 g.; R.B.C., 3,800,000 per c.mm.; reticulocytes, 1%; platelets, 250,000 per c.mm.; W.B.C., 5,700 per c.mm. (neutrophils 78%, eosinophils 2%, lymphocytes 16%, monocytes 4%). The sternal bone marrow was still hypocellular, but the differential count was much improved: blast cells, 3.6%; myeloid cells, 47.6%; erythroid cells, 16.4%; lymphocytes, 13.6%; degenerate cells, 18.8%.

The patient was discharged on August 1 without maintenance therapy. For seven weeks after cessation of treatment he was symptom-free and carried out normal activities. A chest radiograph one week after discharge was normal. In early September relapse occurred and treatment with 6-MP was restarted. The disease was now, however, completely refractory to therapy and the patient died on October 8, 1953. A graphic record of the patient's progress is shown in Fig. 1.

CASE 3: ALEUKAEMIC LYMPHATIC LEUKAEMIA.—A 62-year-old housewife was admitted to the General Infirmary at Leeds on July 23, 1953, with a ten-weeks history of increasing pallor, lassitude, loss of appetite, and dyspnoea on exertion. Temperature 100.4° F. (38° C.). She was anaemic, with large lymph nodes in axillae and groins. The liver was palpable 5 cm., and the spleen 12 cm., below the costal margin. Slight sacral oedema and crepitations at both lung bases were detected. There were no other physical abnormalities. Blood findings were: Hb, 7.8 g.; R.B.C., 2,800,000 per c.mm.; platelets, 119,000 per c.mm.; W.B.C., 1,900 per c.mm. (polymorphs 36%, monocytes 2%, lymphocytes 62%). A percentage of the lymphocytes had nucleoli. Sternal bone marrow was moderately cellular; 66.4% of cells were of the lymphoid series, about half being lymphoblasts. The rest were equally divided between the myeloid and erythroid series. The picture was that of aleukaemic lymphatic leukaemia.

Packed red cells were transfused on July 26, and treatment with 6-MP, 200 mg. daily, was begun on August 7. On August 17 she felt better and her appetite improved. No change was seen on physical examination, but four days later the liver, spleen, and lymph nodes began to get smaller. Dosage was reduced to 100 mg. daily on August 24, and discontinued seven days later, a total of 4.2 g. having been given. Now the spleen was impalpable and the liver edge could be felt only on deep inspiration. A few small, fleshy lymph nodes remained in the axillae. Physical examination was otherwise negative, temperature was normal, and the patient symptom-free.

Unlike in the first two cases, no significant reduction in white cell count followed treatment, and at no stage did it fall below the initial figure. Improved distribution of leucocytes in the peripheral blood was, however, seen within ten days of the start of therapy. The haemoglobin level rose steadily, but there was little increase in platelets. At the end of treatment blood findings were: Hb, 11.2 g.; R.B.C., 3,700,000 per c.mm.; platelets, 100,000 per c.mm.; W.B.C., 3,100 per c.mm. (polymorphs 65%). The bone marrow was less cellular; few lymphoblasts (1.2%) were seen, and 33.6% of the cells were lymphocytes. Erythropoiesis was active and normoblastic, 34.0% of the cells being of this series, and the rest developing granulocytes.

The patient was discharged on September 5 feeling well. When seen ten days later improvement was maintained. The haemoglobin had risen to 12 g. and the platelet count to 275,000 per c.mm. She remained well, with a normal peripheral and bone-marrow blood picture, for seven months, being fully active and living a normal life. Maintenance therapy was not given during the remission, and since relapse in April, 1954, the disease has been refractory to further treatment with 6-MP.

CASE 4.—A man aged 41 was admitted to the General Infirmary at Leeds on April 7, 1954, with widespread purpura, epistaxis, and a large left pleural effusion. The liver and spleen were not enlarged. The blood picture was typical of acute myeloblastic leukaemia, with a total leucocyte count of 129,000 per c.mm., the majority blast cells. As he was very ill an attempt was made to induce an early response to 6-MP by a large initial dose (1 g. over the 24 hours) on April 8, followed by 200 mg. daily thereafter. The leucocyte count fell to 4,800 per c.mm. in four days with much clinical improvement. Treatment was stopped on April 14, when the leucocyte count was 2,000 per c.mm. Improvement continued, the pleural effusion cleared without paracentesis, and the enlarged lymph nodes receded. On May 1 blood findings were Hb, 12.2 g.; W.B.C., 5,400 per c.mm. (polymorphs 65%, lymphocytes 34%, monocytes 1%); platelets, 450,000 per c.mm. Sternal bone marrow: blast cells, 3.2%; myeloid cells, 43.4%; lymphocytes, 12%; erythroid cells, 39.2%; other cell types, 2.2%.

He was discharged on May 8 on a daily maintenance dose of 100 mg. of 6-MP. The remission has now lasted two months.

B. Chronic Myeloid Leukaemia

Of seven patients at different stages of the disease, including one in the acute phase, a varying response was observed in six; the other patient died of cerebral thrombosis a week after starting treatment. Improvement was

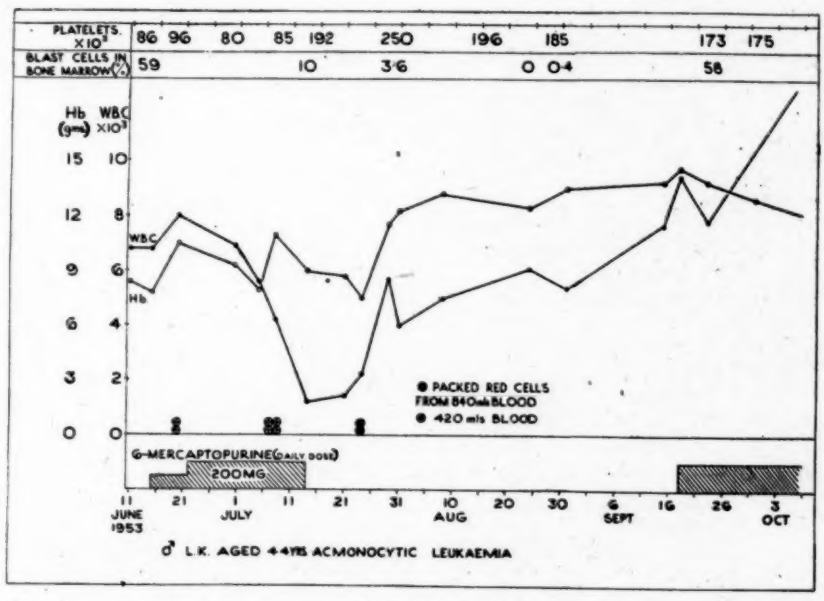


FIG. 1.

assessed on subjective, objective, and haematological changes following treatment.

Subjective improvement—increase in well-being, activity, appetite, and weight—was observed in four cases. Two others showed little subjective improvement, but there were a reduction in size of spleen and a fall in leucocyte count.

Objective improvement—diminution in size of spleen, lymph nodes, etc.—was observed in five cases. In only one case did the spleen fail to regress after prolonged treatment.

The leucocyte count fell in all six cases. In two cases erythropoiesis improved, but in another two no rise in haemoglobin level or red cell count occurred. Two patients had no significant anaemia.

Illustrative Cases

CASE 5.—A 49-year-old man had been well up to the day preceding his admission to the General Infirmary at Leeds on September 25, 1953, when he had a sudden attack of left abdominal pain with vomiting. He had a history of perforated peptic ulcer in 1945 and of partial gastrectomy in 1949. He was a pale, thin man, in obvious pain, and vomited repeatedly during examination. A large, rubbery, mobile lymph node was felt in the left axilla, and the spleen was palpable 8 cm. below the left costal margin. No other clinical abnormalities were found. Blood findings indicated chronic myeloid leukaemia and were as follows: Hb, 9.0 g.; R.B.C., 3,300,000 per c.mm; reticulocytes, 2%; platelets, 300,000 per c.mm.; W.B.C., 128,000 per c.mm. (myelocytes 2%, metamyelocytes 17%, neutrophils 79%, eosinophils 1%, lymphocytes 1%). An occasional nucleated red cell was seen in the peripheral blood film. The sternal bone marrow was hypercellular with a marked preponderance of granular cells.

Treatment with 6-MP was begun on September 28. Within 48 hours of admission the abdominal pain and vomiting ceased, but tenderness of the left upper abdomen persisted for a week. The blood picture was unaltered until October 21, when the leucocyte count fell to 60,000 per c.mm. Two days later it was 44,000 per c.mm., and treatment was stopped, a total dose of 4.4 g. having been given. The spleen, which during the first three weeks had enlarged, became smaller. The patient was discharged on October 28, his progress being regularly followed. His condition remained satisfactory, with a rise in haemoglobin to 11.2 g., and he returned to work the following month. On November 30 the spleen was much larger and the leucocyte count had risen to 56,000 per c.mm. Treatment with 6-MP was restarted in a dose of 100 mg. daily, and after three weeks clinical and haematological improvement was again observed.

In view of previous experience and that of others a maintenance dose of 6-MP seemed necessary if a satisfactory clinical and haematological state was to continue for any length of time, therefore a dosage of 100 mg. and 50 mg. on alternate days was prescribed. On this the patient has remained well, the spleen and lymph nodes have been impalpable and leucocytes and haemoglobin have been kept at normal levels for six months, during which time he has been fully active and doing a normal day's work.

CASE 6.—In a spinster aged 58 chronic myeloid leukaemia was diagnosed in March, 1952. She had no treatment during the following year, but owing to splenic enlargement and discomfort a splenectomy was performed in April, 1953. Deep *x*-ray therapy was then given with temporary improvement. On December 4, 1953, she was admitted to the General Infirmary at Leeds complaining of tiredness, loss of appetite, abdominal pain and distension, and swollen ankles. The liver was enlarged 12 cm. below the right costal margin, and small discrete lymph nodes were felt in the axillae and inguinal regions. Anaemia was not clinically evident. Blood examination revealed: Hb, 12.0 g.; R.B.C., 3,700,000 per c.mm.; platelets, 210,000 per c.mm.; W.B.C., 128,000 per c.mm. (myelocytes 3%, metamyelocytes 12%, neutrophils 84%, lymphocytes 1%).

Treatment with 6-MP, 200 mg. daily, was begun on December 5, but there was a delay of nine days before it took effect. After 12 days the leucocyte count had fallen to 39,600 per c.mm., the patient felt better, and the liver was smaller, being palpable 6 cm. below the right costal margin. Treatment was now stopped, a total of 2.6 g. having been given, and she was discharged with instructions to attend for follow-up. No further improvement occurred during the following week, and treatment with 6-MP was restarted in a dose of 100 mg. daily. On December 30 she felt much better and had gained 7 lb. (3.175 kg.) in weight. The liver was, however, still 6 cm. below the right costal margin, and the leucocyte count had risen to 91,200 per c.mm. Increasing the dose to 150 mg. resulted in a fall in leucocyte count to 15,400 by January 11, when the liver edge was just palpable and she was symptom-free; haemoglobin was 13.5 g. and platelets 250,000 per c.mm.

This patient has been maintained on a daily dose of 50 or 100 mg. of 6-MP for six months, during which time she has been symptom-free and fully active. No objective signs of disease have reappeared and the blood picture has remained satisfactory. The patient's progress is shown graphically in Fig. 2.

CASE 7.—A 56-year-old housewife was admitted to St. James's Hospital, Leeds, on December 18, 1953, with a seven-years history of myeloid leukaemia treated by several courses of deep *x*-ray therapy, the last in October, 1953. Her main complaints were repeated vomiting, a dragging sensation in the left abdomen, loss of weight, sweating, and epistaxis. The spleen was firm and tender and extended to 15 cm. below the left costal margin, and the liver was palpable 2 cm. below the right costal margin. Blood examination showed the following: Hb, 8.2 g.; R.B.C., 2,300,000 per c.mm.; platelets, 225,000 per c.mm.; W.B.C., 152,000 per c.mm. (blast cells 8.5%, myelocytes 25.5%, metamyelocytes 8.0%, polymorphs 35.8%, lymphocytes 17.5%, monocytes 2%). Sternal bone marrow was hypercellular, with blast cells 74.0%, myeloid cells 21.6%, erythroid cells 3.2%, lymphocytes 0.8%, and other cells 0.4%. The findings were characteristic of the acute terminal phase of chronic myeloid leukaemia.

Treatment with 6-MP, 200 mg. daily, was started on December 18, and on December 23 blood was transfused,

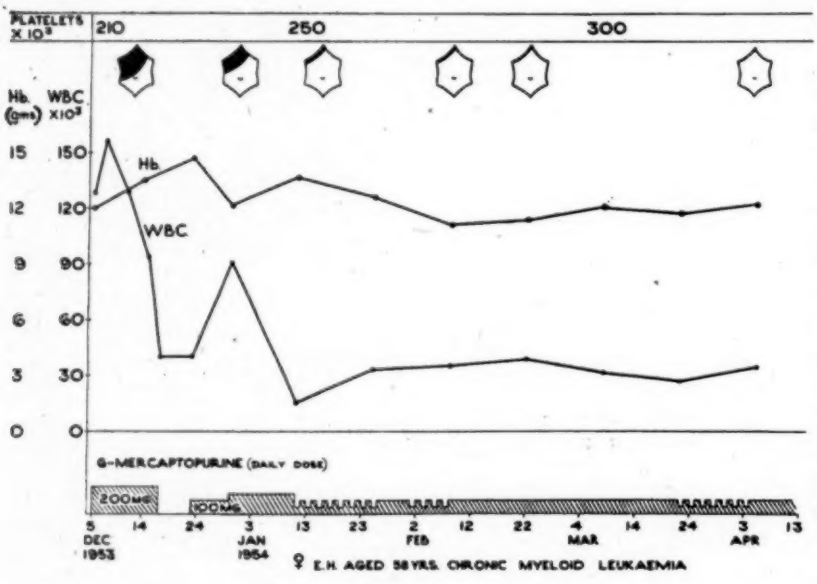


FIG. 2.

raising the haemoglobin level to 11.3 g. per 100 ml. The leucocyte count fell after three days' treatment, and by two weeks had reached 13,000 per c.mm.; the patient felt stronger, vomiting and sweating had ceased, the liver was impalpable, and the spleen 9 cm. below the left costal margin. The dose of 6-MP was reduced to 100 mg. daily on January 2, and this was continued until January 14, when treatment was stopped, a total of 4.1 g. having been given in 27 days. By now the leucocyte count had fallen to 300 per c.mm., and the haemoglobin to 7.5 g., and the spleen was just palpable. More blood was transfused on January 22, and this raised the haemoglobin level to 11.7 g. The bone-marrow picture was also much improved: blast cells, 8.5%; myeloid cells, 47.5%; erythroid cells, 18.5%; lymphocytes, 24%; other cells, 1.5%. She was now well enough to get up, and although the leucopenia persisted for a month no complications resulted. The haemoglobin level was maintained without further blood transfusion, and clinical examination failed to reveal any of the usual findings of leukaemia. On February 2 she was discharged, and when next seen two weeks later she was symptom-free and doing a full day's domestic duties. Blood examination showed: Hb, 12.0 g.; R.B.C., 4,000,000 per c.mm.; platelets, 200,000 per c.mm.; W.B.C., 4,400 per c.mm. (polymorphs 80%, lymphocytes 20%). She was put on a daily maintenance dose of 50 mg. of 6-MP, and remained in good health for four and half months after completing the initial course of treatment. Relapse then occurred, and the disease was found to be resistant to further treatment with 6-MP. She died on June 26, 1954.

C. Chronic Lymphatic Leukaemia

Two patients (aged 73 and 56 years) with chronic lymphatic leukaemia showed no clinical or haematological evidence of improvement after one month's treatment with 6-MP.

D. Miscellaneous Group

Two patients with multiple myeloma, and one with erythroderma considered to be due to a reticulosis of undetermined type, failed to benefit from a month's treatment with 6-MP. One patient with mycosis fungoides appeared to be temporarily improved.

TOXICITY

An important property of 6-MP is its low toxicity. Apart from depressing bone-marrow function it has not resulted in any definite toxic side-effects in the present series. Burchenal has stated (Burchenal, Murphy, *et al.*, 1953) that gastro-intestinal symptoms may occur; but, whereas there has been vomiting in some of the cases now reported, on no occasion was it definitely attributable to the drug, nor did it necessitate interrupting treatment. Ulceration of the mouth, which is so common after treatment with aminopterin or amethopterin, was not observed. Severe thrombocytopenia attributable to 6-MP occurred in only one case—of multiple myeloma—but on no occasion was there haemorrhage. Haemorrhage due to overdosage with 6-MP has, however, been described by Burchenal and his co-workers, and must always be considered as a possible complication. Leucopenia is expected to follow treatment of acute leukaemia, and should not give rise to undue anxiety. No evidence was seen of megaloblastic erythropoiesis, which is an occasional sequel of anti-folic-acid treatment.

DISCUSSION

A study of the results obtained in this limited series supports the finding of Burchenal and others that 6-MP may produce temporary remissions in a percentage of cases of acute leukaemia and modify the course of chronic myeloid leukaemia. Chronic lymphatic leukaemia, however, appears to be unaffected by it.

Until a much larger number of patients have been treated no definite information can be obtained as to age group and morphological type of acute leukaemia likely to be most responsive to treatment with 6-MP. All that can be said is that adults as well as children have had remissions following treatment, and that remissions have been noted in the lymphoblastic, myeloblastic, and myelo-monocytic types of acute leukaemia. Thus 6-MP may be more versatile in its action than aminopterin and amethopterin, which are generally accepted as ineffective in adults and most effective in acute lymphoblastic leukaemia. As with other chemotherapeutic agents used in the management of acute leukaemia (Fountain, 1954), the remissions in patients who respond are only temporary, and, although a second response may occur, the disease gradually becomes resistant to further treatment.

A delay of 7 to 28 days was usual before the drug took effect, which suggests that four patients who died within the first week of treatment had received an inadequate therapeutic trial. In two cases a fall in leucocyte count with clinical improvement occurred, however, within a few days of starting treatment. One patient (Case 7), in the acute terminal phase of chronic myeloid leukaemia, received a routine course of treatment. The other (Case 4) had an extremely acute form of myeloblastic leukaemia with considerable haemorrhagic manifestations. In the hope that the rate of action of the drug would be increased an initial "loading" dose of 1 g. in the first 24 hours was given. Dramatic clinical and haematological improvement followed within the next four days. Although its value remains to be proved—another patient failed to respond rapidly to large doses—such a dosage scheme seems worth trying, as it is obvious that with such a disease as acute leukaemia the rapidity of action of the therapeutic agent is of prime importance. It may be of interest that both patients who responded rapidly to 6-MP had a high initial leucocyte count (over 100,000 per c.mm.), the predominant cell in each case being the primitive blast cell.

Whether patients who experience a complete remission should receive a daily maintenance dose of 6-MP remains to be answered, but from the limited data in this series it seems likely that maintenance therapy may not greatly prolong the remission. Continuous therapy seems essential in chronic myeloid leukaemia if the beneficial effect of the drug is to be maintained, for it has been my experience that in its absence clinical and haematological relapse may follow within a month of stopping treatment.

CONCLUSION

It has been shown that a new compound, 6-mercaptopurine, allied to the folic-acid analogues has been discovered with which dramatic remissions may be obtained in a percentage of cases of acute leukaemia. Unlike aminopterin and amethopterin, 6-MP has a low toxicity and can be used with little danger of added discomfort to the patient—an important consideration in the management of cases of leukaemia. That the remissions are only temporary suggests that the value of 6-MP as a research compound will at present outweigh its clinical usefulness. However, with the knowledge that aminopterin and amethopterin, A.C.T.H. and cortisone, and 6-MP may all produce clinical and haematological remissions in acute leukaemia, it seems desirable to give patients the advantage of such chemotherapy. Symptomatic relief may be obtained, and by sequential use these drugs may offer several months of useful life.

Although more patients with chronic myeloid leukaemia must be treated before the ultimate value of 6-MP is known, initial observations suggest that it will have its place in the management of this disease. The experience of Burchenal and his colleagues that 6-MP benefited two patients in the acute terminal phase of the disease has been supported by a case in this series, and it may be that one of its main uses in chronic myeloid leukaemia will be in the later acute stage of the disease.

SUMMARY

A purine antagonist, 6-mercaptopurine, has been shown to produce complete clinical and haematological

remissions in five out of thirteen patients, of various ages, with acute leukaemia, and partial remissions in two others. The remissions were only temporary, and resistance to further therapy with 6-MP eventually resulted.

Six patients with chronic myeloid leukaemia showed a varying response. One patient in the acute terminal phase had a remission lasting four and a half months.

Two patients with chronic lymphatic leukaemia, two with multiple myeloma, and one with reticulosis of the skin did not respond, while one patient with mycosis fungoides obtained some improvement.

6-MP is of low toxicity and no serious complications have followed its use.

I wish to thank the consultant physicians of the Leeds Hospitals for permission to study patients under their care, and also Dr. D. H. Collins and Dr. W. Goldie and the staff of their laboratories at the General Infirmary and St. James's Hospital, Leeds. I am indebted to Professor R. E. Tunbridge for his advice and criticism.

6-Mercaptopurine was initially supplied through the kindness of Dr. D. S. Searle, Medical Director, Burroughs Wellcome & Co. Inc., Tuckahoe, New York, U.S.A., and later by Dr. F. Prescott, Clinical Research Director, Burroughs Wellcome, London, England.

REFERENCES

Burchenal, J. H. (1954). Personal communication.
—— Bendich, A., Brown, G. B., Elion, G. B., Hitchings, G. H., Rhoads, C. P., and Stock, C. C. (1949). *Cancer*, **2**, 119.
—— Johnston, S. F., Burchenal, J. R., Kushida, M. N., Robinson, E., and Stock, C. C. (1949). *Proc. Soc. exp. Biol. (N.Y.)*, **71**, 381.
—— Karnofsky, D. A., Kingsley-Pillers, E. M., Southam, C. M., Myers, W. P. L., Escher, G. C., Craver, L. F., Dargeon, H. W., and Rhoads, C. P. (1951). *Cancer*, **4**, 549.
—— Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, T. C., Leone, L. A., Karnofsky, D. A., Craver, L. F., Dargeon, H. W., and Rhoads, C. P. (1953). *Blood*, **8**, 965.
Falco, E. A., Hitchings, G. H., Russell, P. B., and Vanderwerff, H. (1949). *Nature (Lond.)*, **164**, 107.
Farber, S., Diamond, L. K., Mercer, R. D., Sylvester, R. F., jun., and Wolff, J. A. (1948). *New Engl. J. Med.*, **238**, 787.
—— Foley, G. E., Dawning, V., Appleton, R., and King, J. (1953). *Proc. Amer. Ass. Cancer Res.*, **1**, 15.
Fountain, J. R. (1954). *Edinb. med. J.*, **61**, 69.
Hitchings, G. H., Falco, E. A., Vanderwerff, H., Russell, P. B., and Elion, G. B. (1952). *J. biol. Chem.*, **199**, 43.
Proceedings of the Second Conference on Folic Acid Antagonists in the Treatment of Leukaemia (1952). *Blood*, **7**, Supplement.

ERYTHRAEMIC MYELOSIS TERMINATING IN ERYTHROLEUKAEMIA

BY

J. R. HINDMARSH, M.D., M.R.C.P.
Consultant Physician

AND

T. A. J. WICKHAM, M.B.
Assistant Pathologist, Bournemouth and East Dorset Group
(From the Poole General Hospital, Poole, Dorset)

Malignant hyperplasia of the erythron, analogous to leucoblastic proliferation in leukaemia, was first described by Copelli (1912) and later defined as a pathological entity by Di Guglielmo (1923, 1926, 1937) when he recorded three cases as examples of true "erythraemic myelosis." These cases, with others published on the Continent, have been exhaustively reviewed by Di Guglielmo (1945, 1946) and Leitner (1949).

As with leukaemias, acute and chronic forms are recognized. Acute erythraemic myelosis (Di Guglielmo, 1945), pursuing a fatal course of one or two months, presents with severe anaemia, irregular fever, splenomegaly, slight hepatomegaly, and erythroid hyperplasia, with atypical erythroblasts in the blood, many of which fail to mature. The chronic form (Duesberg, 1940; Heilmeyer and Schöner, 1941; Di Guglielmo and Quattrin, 1942) runs a longer course, up to two years, and the circulating erythroblasts are orthochromatic and less atypical.

In this country four examples of the chronic form appear to have been recognized, three of which have been published in Britain (Israëls, 1939; Neumark, 1948; Emery, 1951; Mackenzie and Stephenson, in *Blood*, 1952). A subacute form, terminating in acute granulocytic leukaemia, has also been recorded (Discombe and Nickol, 1954).

If in the case described below the patient had died within the first two months a diagnosis of acute erythraemic myelosis would have been accepted, but repeated blood transfusions sustained life for a further four months, during which the erythroleukaemic nature of the disease became manifest. In this respect our case closely resembles those of Verloop, Deenstra, and van der Hoeven (1952) and Discombe and Nickol (1954), lending support to the theory that erythraemic myelosis and erythroleukaemia are probably unusual variants in the onset of acute leukaemia.

Case Report

A single woman aged 30 gave up work in a soda-water factory early in August, 1953, because she felt very tired and breathless on the slightest exertion. Two weeks later she developed lumbar pain, headache, and nausea with vomiting.

On admission on August 25 she was very pale, had a temperature of 102° F. (38.9° C.) and fetid breath but no ulceration of the gums or fauces. The liver was palpable and the spleen descended five fingerbreadths in inspiration. There was no relevant personal or family history. Clinically she was considered to be a case of leukaemia, but subsequent blood and marrow pictures (see below) indicated erythraemic myelosis.

Owing to the severe anaemia she was given repeated blood transfusions, 26 pints (14.8 litres) in all, over a period of six months, the highest haemoglobin achieved being 78% (12.4 g.). Transient improvement followed each transfusion; vomiting ceased, the appetite returned, and the temperature subsided.

As her condition could not be maintained despite transfusions, liver, cyanocobalamin ("cytamen"), iron, vitamins, folic antagonists, and corticotrophin, it was decided to remove her spleen. This was done without incident on December 18. Improvement followed splenectomy, the haemoglobin remaining at 66% (10.5 g.), and in January, 1954, she was sent home on corticotrophin. She was now apyrexial, eating well, and gaining weight.

She was readmitted on February 19, 1954, with recurrent vomiting and pyrexia and the haemoglobin had now fallen to 42% (5.7 g.). Further transfusions had little effect and she continued to go downhill. Early in March a large gluteal abscess, following an injection of corticotrophin, was evacuated and 11 oz. (320 ml.) of pus obtained. The wound continued to discharge, and shortly before death on March 23 the haemoglobin had fallen to 16% (2.5 g.). Transfusions were now withheld, as she was obviously in the terminal stages of her illness.

Investigations

General.—Histamine-fast achlorhydria. Urobilinogen excess in urine but no haemosiderin in centrifuged deposit. Bile pigments scanty. Serum bilirubin, 1.2 mg. per 100 ml.

Blood.—Three representative blood counts are set out in the Table. Red cells showed marked anisocytosis, poikilocytosis, and moderate polychromasia. Platelets were scanty

Peripheral Blood

	Week of Admission	Week after Splenectomy	Week before Death
Haemoglobin	5·4 g. (34%)	10·5 g. (66%)	2·5 g. (16%)
Erythroblasts	15,370	21,000	100,600
Leucocytes	2,400	18,800	117,000
Myelocytes	1%	8%	5%
Metamyelocytes	4%	11%	7%
Polymorphs	29%	51%	19%
Eosinophils	1%	2%	1%
Lymphocytes	53%	20%	2%
Monocytes	12%	3%	23%
Promonoctyes	—	—	34%
Stem cells	—	5%	9%

at all times. Reticulocytes 5.5% during cyanocobalamin therapy. Red-cell fragility was not significantly increased and tests for underlying haemolytic mechanisms were negative. Cold agglutinins were absent.

Sternal Marrow Punctures.—September 11, 1953 :—Easily aspirated, densely cellular, hyperplastic marrow—over 95% of the nucleated cells being erythrocyte precursors in which megalo-, macronormo-, and normo-blastic erythropoiesis were evenly represented. Multipolar mitoses and nuclear-cytoplasmic "ripening" dissociation were present in minor degree. November 22 :—Same dense cellularity, but granulocytes now numbered 24.5% and red-cell precursors had fallen to 60%. As before, megakaryocytes were very scanty. Erythroid mitoses were still plentiful, but there appeared to be fewer mitotic abnormalities. An increase in megaloblasts was attributed to antifolic therapy. February 23, 1954 :—A hypocellular marrow aspirated with difficulty. Monocytes and their precursors now predominated. Some of the mature forms contained red cells.

Splenectomy.—December 18, 1953 :—The spleen weighed 41 oz. (1,120 g.). It was flabby, bright red in colour, and contained three recent infarcts. Histologically the Malpighian bodies were small and widely separated. The sinuses were filled with erythroblasts, but the reticulo-endothelial lining appeared to be normal and unproliferative. A few iron-laden macrophages and small foci of granulopoiesis were present.

Liver Biopsy.—December 18, 1953 :—Small centres of granulopoiesis, normoblasts in the portal tracts, and a sprinkling of haemosiderin in the periphery of the lobules.

Necropsy Report

Necropsy performed 16 hours after death. Several greyish macules on trunk and a few petechiae on forearms. The heart was slightly enlarged, very pale and flabby, and contained greyish-pink creamy blood. The liver (2,621 g.) was pale and yellowish grey. Two enlarged, soft, greyish lymph nodes were found at the hilum. The kidneys were enlarged and showed scattered wedges of homogeneous yellowish-grey colour with little demarcation between cortex and medulla. The marrow of sternum, ribs, vertebral bodies, and left femoral shaft was uniformly grey in colour. Several pea-sized cherry-red nodules were found in the dura over the left cerebral vertex but the brain was normal. Apart from bloodlessness the other organs appeared normal.

Histology.—The bone marrow showed a dense uniform cellularity with a few widely scattered islands of erythroblasts. The predominating cell had a round or oval vesicular nucleus with a thin rim of cytoplasm. Mitoses were scanty. Lymph-node architecture was partially disorganized, the surviving follicles at the periphery being small and devoid of germinal centres. The invading cells were a mixture of those seen in the marrow and normoblasts. The liver cells were compressed and loaded with haemosiderin in the outer and middle zones of the lobules and there were numerous monocytoid cells and normoblasts in the portal tracts.

The dural nodules, skin, stomach, intestines, heart, kidney, adrenals, thyroid, pituitary, uterus, and ovaries all showed infiltration in varying degree by cells indistinguishable from those in the marrow.

Discussion

In the evaluation of this and other cases presented as acute erythraemic myelosis the greatest difficulty lies in excluding various forms of haemolytic anaemia. The presence of atypical erythroblasts with abnormal nuclei is among the features characteristic of the disease (Di Guglielmo, 1946), the typical failure of maturation in the erythroblasts of our cases being evidenced by the low reticulocyte counts.

Although deaths from erythraemic myelosis still occur (Emery, 1951 ; Schwartz and Critchlow, 1952) evidence accumulates to suggest that the longer the patient lives the more likely is acute leukaemia to develop. Gradations and transitions between erythraemic myelosis, erythroleukaemia, and myeloid leukaemia have been noted by Blackburn and Lajtha (1951) and by Martin and Bayrd (1954). Our case, in developing a monocytic element, constitutes a departure from the usual myeloblastic finale, but this may have been of Naegeli type, the so-called "monocytic phase of myeloid leukaemia." However, in describing the Schilling type, Wintrobe (1951) states that some of the cases have shown a widespread hyperplasia of monocytic cells in the connective tissue, especially about the blood vessels. It is of interest that the same perivascular reticulo-endothelial hyperplasia has been noted in several cases of erythraemic myelosis, Di Guglielmo himself describing transitional forms between reticulum cells and erythroblasts as a feature of the disease. Moreover, many cases, critically reviewed and accepted as erythraemic myelosis, have shown a frank monocytosis.

If we accept Dameshek's view that marrow reaction may be non-specific and provoke response along multiple channels, or Downey's modification of the neo-unitarian theory, ascribing toti-potentiality to the reticulo-endothelial cell, then we may conveniently regard erythraemic myelosis, erythroleukaemias, and leukaemias as manifestations of a fundamental "stem-cell" derangement and satisfactorily group them together as a reticulo-endotheliosis.

Summary

A woman aged 30 died six months after the onset of a profound resistant anaemia characterized, in the early stages, by erythroblastaemia, leucopenia, and erythroblastic hyperplasia in the marrow. A diagnosis of acute erythraemic myelosis (Di Guglielmo's disease) was made.

Following splenectomy the picture changed to one of erythroleukaemia, the leukaemic element being monocytic and probably of Naegeli type.

The relationship between erythraemic myelosis, erythroleukaemia, and leukaemia is briefly discussed.

We wish to thank Mr. F. P. Forrest, surgeon, Poole General Hospital, for performing the splenectomy and liver biopsy; Dr. C. H. D. Bartley, Wimborne, for tending the patient during her brief period at home after splenectomy; and Messrs. C. J. Cooper and J. Power for technical assistance.

References

Blackburn, E. K., and Lajtha, L. G. (1951). *Blood*, **6**, 261.
Copelli, M. (1912). *Pathologica*, **4**, 460.
Di Guglielmo, G. (1923). In A. Ferrata's *Le Emopatie*. Milan.
—— (1926). *Boll. Soc. med.-chir. Pavia*, **40**, 665.
—— (1937). *Boll. Soc. med.-chir., Catania*, **5**, 588.
—— (1945). *Le Malattie Eritremiche*. Rome.
—— (1946). *Rev. Hémat.*, **1**, 355.
—— and Quattrin, N. (1942). *Haematologica*, **24**, 1.
Discombe, G., and Nickol, K. (1954). *J. clin. Path.*, **7**, 211.
Duesberg, R. (1940). *Klin. Wschr.*, **19**, 417.
Emery, J. L. (1951). *J. Path. Bact.*, **63**, 395.
Heilmeyer, L., and Schöner, W. (1941). *Dtsch. Arch. klin. Med.*, **187**, 225.
Israëls, M. C. G. (1939). *J. Path. Bact.*, **48**, 299.
Leitner, S. J. (1949). *Bone Marrow Biopsy*, p. 166. English translation, edited by C. J. C. Britton and E. Neumark. Churchill, London.
Mackenzie, I., and Stephenson, A. G. (1952). *Blood*, **7**, 927.
Martin, W. J., and Bayrd, E. D. (1954). Ibid., **9**, 337.
Neumark, E. (1948). In S. J. Leitner's *Bone Marrow Biopsy*, p. 167. English translation. Churchill, London.
Schwartz, S. O., and Critchlow, J. (1952). *Blood*, **7**, 765.
Verloop, M. C., Deenstra, A., and Hoeven, L. H. van der (1952). Ibid., **7**, 454.
Wintrobe, M. M. (1951). *Clinical Haematology*, 3rd ed., p. 877. Kimpton, London.

SOME ADVANCES IN THE SURGERY OF THE OESOPHAGUS*

BY

R. H. FRANKLIN, F.R.C.S.

Consulting Surgeon, Hammersmith Hospital and Kingston Hospital; Senior Lecturer in Surgery, Postgraduate Medical School of London, W.12.

It is my intention to give a picture of the present positions of some of the pathological conditions met with in the oesophagus. As regards cancer I propose to confine my remarks to the condition as it affects the thoracic and abdominal parts of the gullet. The results obtained at the present time are disappointing until we remember the hopeless nature of the condition only a few years ago. The first successful removal of a thoracic oesophagus was described by Torek in 1913, and no further success was recorded until Grey Turner reported a case in 1933, the oesophagus in this patient being removed by the collo-abdominal or pull-through method. In 1933 Ohsawa, in Japan, had recorded his experiences with 101 patients in the preceding seven years. In 18 of these the tumour involved the lower end of the oesophagus or cardia, and resection was carried out with immediate anastomosis. No fewer than eight of these patients survived. This publication was in Japanese and did not attract general notice at the time. The surgeons who were then interested in the oesophagus mostly aimed at removing the gullet at the first operation, and, in the rare event of the patient surviving, restoring continuity by means of an antethoracic oesophagus.

In 1937 Nissen, of Basle, reported a case of transthoracic resection of the cardiac end of the stomach and lower oesophagus for a simple ulcer, with an immediate anastomosis. This was probably the first successful anastomosis of this type either in Europe or in the Americas, and I would like to take the opportunity of drawing attention to this very early success although it was carried out for a non-malignant condition. When we feel depressed to-day we should remember that when Grey Turner delivered the Macewen Lecture in 1939 he referred to the remarkable experience of Dr. Garlock, of New York, "who in the last two years has had no less than three consecutive cases in which he was able to remove a malignant oesophagus by the transthoracic route and with the immediate recovery of the patient."

The conception of an immediate anastomosis has been accepted and all the operations on the oesophagus in recent years have aimed at this. There have been variations in the method of approach and in the means by which continuity is restored, and it is clear that the level of the growth determines which operation is suitable. In 1946 Ivor Lewis described the operation in which the stomach is mobilized through an abdominal incision; the oesophagus is then explored, and, if possible, resected through the right side of the chest. Continuity is restored by bringing the stomach up to the cut end of the oesophagus.

Allison and Borrie (1949) have advanced the surgery of the cardiac end of the stomach by drawing attention to the place for radical block excision of the stomach in these cases.

*Annual address delivered to the Institute of Laryngology and Otology on October 15, 1954.

Diagnosis

X-ray examination is essential in all cases of dysphagia, and it is usually necessary to carry out oesophagoscopy. Oesophagoscopy occasionally discloses cases in which the diagnosis of carcinoma would otherwise have been missed, and, what is more gratifying, a number of patients are encountered in whom the symptoms and the radiological appearance are strongly suggestive of cancer but who later prove to be suffering from benign conditions. This fact must be remembered when successful results are claimed from irradiation in the absence of histological confirmation of the diagnosis (Figs. 1 and 2).

FIG. 1.—The extent of the malignant stricture has been determined by placing the patient in the Trendelenburg position after some of the contrast medium has passed the stricture.

FIG. 2.—An irregular filling defect of the middle of the thoracic oesophagus closely simulating cancer but which was proved to be benign.

Method of Treatment

The only hope of radical cure is that offered by surgical excision. Irradiation is occasionally a satisfactory palliative treatment, but even for this purpose it has serious disadvantages in that fistula formation is sometimes precipitated. It is necessary to keep an open mind on the question, because recent methods of application in which the patient is rotated during treatment have given better results.

Another form of palliation, successfully carried out by Negus, is that of implantation of the growth with radon seeds through the oesophagoscope. This method requires a very high degree of endoscopic skill, and it deprives the patient of the possibility of a successful radical removal. It should therefore not normally be advised unless inoperability can be inferred or deduced without exploration.

Souttar tubes are occasionally of great value in those patients who are not in a fit condition for any form of exploratory thoracotomy. The drawback of the Souttar tube is that, in the very case in which it would be most suitable and useful, difficulties are encountered in its introduction.

Inoperable growths can be short-circuited. This method has particular application in the middle third of the oesophagus, where a comparatively small growth may be firmly fixed to the root of the lung.

Recently a great interest has been taken in the use of plastic tubes either to replace a portion of the oesophagus

which has been removed or to effect a short-circuit. My own objection to this method is that if resection is feasible it is usually more satisfactory to restore continuity by means of either the small bowel or the stomach. A growth at the thoracic inlet presents a difficult problem, being too low for the Trotter type of procedure and too high to be dealt with entirely from the thorax. In such a situation a plastic tube is a possible way out of the difficulty, but if the patient is fit enough it is better to resect the growth and carry out cervical oesophago-gastrostomy.

All cases of cancer of the oesophagus should be given the chance offered by operation if their condition can be sufficiently improved by proper preparation. The immediate mortality has been reduced enormously by attention to this one detail. The essential part of this pre-operative treatment is to spend two or three weeks in building up the patient's nutrition by means of a fortified liquid diet consisting of: 2 eggs; 2 oz. (57 g.) of sugar; 1 teaspoonful of salt; 2 oz. of National dried milk (full cream); 1 oz. (28 g.) of butter; brandy flavouring, if desired; 2 pints (1,140 ml.) of milk. Four pints (2–3 litres) in the 24 hours should be the aim. It is essential that the patient has a jug of this mixture constantly by his side, and he should be encouraged to sip it whenever he feels able to do so. It is quite useless to give him a glass of milk three or four times a day and take it away again at the end of a "so-called" meal-time. Fruit juice, alcohol, and meat extracts, etc., may be given separately to provide the patient with a little variety in flavour.

Occasionally when the patient is first seen there is dysphagia even with liquids, and a gastrostomy has to be carried out as an emergency. Usually after a few days it will be found that the oedema around the growth has settled down and will allow mouth-feeding with liquids to be resumed. As his nutrition improves the patient usually feels stronger and he should be encouraged to walk, to practise breathing exercises, and generally to improve his condition to the utmost of his power.

Choice of Operation

The choice of operation is determined by the site of the growth.

Growths at the Cardia.—These are best approached by a left-sided abdomino-thoracic incision, removing the eighth rib and dividing the diaphragm and the costal margin. The stomach and lower part of the oesophagus are removed by a total block dissection, including the great omentum, spleen, tail of the pancreas, and the lesser omentum. This is the procedure which has been so well described by Allison and Borrie (1949). Such an extensive operation is accompanied by less shock than would be imagined. The immediate post-operative results are sometimes disappointing in that the patient feels very distended even after small meals and he may suffer from anaemia; but it has been my experience that a number of these patients improve considerably some months after operation.

Growths between Diaphragm and Arch of the Aorta.—A left-sided abdomino-thoracic approach is made as described above. An intercostal incision is now made in the fourth or fifth interspace after the scapula has been drawn forward. The improved exposure by the two incisions makes it relatively easy to excise the lower two-thirds of the oesophagus. Continuity is restored by bringing the stomach above the arch of the aorta.

Growths of Middle Third of Oesophagus.—Growths at this level are often closely attached to the arch of the aorta and to the right pleura. An approach from the left side may open both pleural cavities and cause uncontrollable bleeding from the vena azygos arch. For this reason the right-sided approach is used for growths in this situation after mobilization of the stomach through an abdominal incision. This type of growth is sometimes treated by a palliative short-circuit, bringing the fundus of the mobilized stomach above the level of the growth and making a side-to-side anastomosis. The palliative operation may be carried out from the left or right thoracic approach.

Mortality of Operations for Cancer of the Thoracic Oesophagus

The immediate mortality resulting from these operations is shown in the Table, which is composed of all the cases which came under my care at Hammersmith Hospital in the years 1951, 1952, and 1953. It should be noted that very few patients have been denied an exploration.

Cancer of the Thoracic Oesophagus and Cardia, 1951–3

	No. of Cases	Deaths
Resection of growth and anastomosis above arch of aorta	12	4
" " " " " below " " "	20	9
Palliative short-circuit	8	1
Excision of middle third and introduction of plastic tube	1	1
Exploration only	3	1
No operation	7	5
Souttar tube	2	1
Gastrostomy only	1	—
	54	22

From the point of view of long-term survival the results are disappointing, although one patient is still enjoying good health seven years after resection. It must be remembered that many of the patients are elderly at the time of operation, the oldest in the series being 84 years of age when she underwent a successful operation. Perhaps the most important result of excision of a thoracic growth is that the patient is able to resume a normal life and to take a normal diet, and if recurrences develop dysphagia is not necessarily a symptom.

Reflux Oesophagitis

The occurrence of benign strictures of the oesophagus, unassociated with the swallowing of corrosives, has been noted for many years and diaphragmatic hernia, pregnancy, and excessive vomiting from various causes have been recognized as factors in the production of these strictures. Brown Kelly (1930) described the occurrence of ascending strictures of the oesophagus in association with diaphragmatic hernia in 1930, and Vinson (1923) drew attention to the occurrence of stricture of the oesophagus during pregnancy in 1923. The association of anaemia and diaphragmatic hernia has been recognized for many years, but it is only recently that the cause of the anaemia has been clearly understood. The contributions of Allison, Barrett, and others have thrown light on the pathological process in this condition. The term "reflux oesophagitis," suggested by Barrett (1950), should be generally employed.

FIG. 3.—"Rolling" hernia in which there is a chronic gastric ulcer in the thoracic portion of the stomach.

The underlying cause appears to be a failure of the sphincteric mechanism at the lower end of the oesophagus, which allows free regurgitation of gastric contents into the gullet, with consequent irritation. The causes for failure of the cardiac sphincter are various, but one of the most important is undoubtedly the presence of a hiatal hernia in which the cardia is displaced into the chest, with interference with the angle of insertion of the oesophagus into the stomach. A para-oesophageal hernia, on the other hand, in which a

large part or almost the whole of the stomach may be displaced into the chest, while the cardia remains in its normal position, will not affect the sphincter, and consequently oesophagitis is not produced. A combination of these two types occurs, known as a rolling hernia, in which the oesophagitis is a frequent complication (Fig. 3).

Results of Regurgitation of Gastric Juice

Superficial ulceration takes place which tends to heal and break down again. This ulceration produces spasm in the muscular coats of the oesophagus and later cicatricial contraction. Both processes lead to a gradual shortening of the oesophagus and to stricture formation.

Symptoms

Pain, dysphagia, and symptoms due to haemorrhage may all occur, together or separately, and the severity of each symptom may vary from a slight disturbance to a major illness. The pain is characteristically retrosternal and is produced by any posture or movement which encourages regurgitation. Movements such as stooping down to tie up the shoes or lying flat in bed will all tend to aggravate the pain. Besides being felt as a heartburn or retrosternal pain, radiation often occurs down one or both arms and up into the angle of the jaw. When this happens a diagnosis of cardiac pain is sometimes made, or if the distribution is very extensive the symptoms are often attributed to necrosis. The spastic contractions of the circular muscle and later the cicatricial changes will each produce dysphagia, although the spastic element will tend to improve spontaneously if the oesophagitis becomes less. The dysphagia varies from a subjective feeling of food sticking to inability to take any food whatsoever. The bleeding is usually intermittent and insidious, and in fact is suspected only when the patient is found to be grossly anaemic. Massive haemorrhage occurs occasionally in these patients, and is usually due to the fact that the stomach has been drawn up into the chest as part of the pathological process and a chronic gastric ulcer has developed in the thoracic stomach.

The diagnosis of the condition is made by *x*-ray and oesophagoscopic examination. It may be confused on occasion with carcinoma on the one hand and true cardiospasm or achalasia on the other.

Treatment

The heartburn from which these patients suffer is often attributed to duodenal ulceration, and the treatment prescribed may be sufficient to relieve the symptoms. In any event, the duodenal ulcer patient who has a high gastric acidity and whose stomach possibly empties slowly owing to spasm at the pylorus will also suffer from reflux oesophagitis should his cardiac sphincter be incompetent. Where pain and anaemia are the most marked features medical management should be given a trial in the first instance. The regime adopted should be exactly that used in treating a duodenal ulcer, with the difference that great emphasis must be placed on avoiding all postures and movements which encourage regurgitation. This regime is sufficient to improve a considerable number of patients. Even if there is some degree of stricture formation, a strict medical regime together with dilatation of the oesophagus may prove effective, but dilatation by itself must never be used in these patients because the result will be fresh stricture formation at a higher level.

If simple measures fail or severe stricture formation is present, or the presence of an ulcer in a thoracic stomach is proved or suspected, operation must be undertaken. The nature of the operation depends on the changes which have occurred in the oesophagus and whether it is possible to restore the anatomical arrangement at the hiatus to normal. If this is the case an operation aimed at replacing the stomach in the abdomen and retaining it there by suturing the phrenico-oesophageal ligament to the undersurface of the diaphragm is the basis of the procedure. This ligament, described by Allison (1951), is not recognized by some surgeons, but there is usually no difficulty in demonstrating its presence and using it in the manner described. Decreasing the size of the actual hiatus is of little importance, because the opening in any event is an elastic one and its increase in size is brought about by the cone of stomach forcing its way upwards. If the stomach is kept down, the crus of the diaphragm will conform to the lower end of the oesophagus. As an adjunct to this form of repair I make a point of dividing both vagi to decrease the gastric secretion. To overcome the ill effects of the vagotomy the pyloric sphincter is divided. This procedure may disclose a number of cases of unsuspected duodenal ulcer.

If there is a long stricture present or a chronic ulcer has formed in the thoracic stomach, simple restoration of the anatomy is no longer effective and resection must be undertaken. The extent of the resection and the method of restoring continuity will vary according to the particular circumstances.

Hiatal Hernia and Reflux Oesophagitis in Infants

Infants present a difficult problem in that the symptoms of reflux oesophagitis may be confused with those of pyloric obstruction, and an operation for the latter condition is sometimes carried out. In some patients there seems no doubt that pyloric spasm makes the symptoms of reflux oesophagitis more apparent. The cardiac sphincter in infants is not well developed, and if too large a feed is given regurgitation will take place without any difficulty. It seems that in certain circumstances ulceration is produced either because the gastric contents are more irritating than usual or because the oesophageal epithelium is unduly sensitive. Once oesophagitis has started a vicious circle is set up and spasm and actual cicatricial contraction may occur, producing shortening of the oesophagus and stricture formation. It seems that the process can be arrested and reversed and the stomach may return to its normal abdominal position.

Treatment for these infants should again be medical in the first instance, posture being of great importance. Occasionally a gastrostomy may be called for. Anatomical repair of the hernia in the sense that the stomach is held down in its proper position, as has already been described, may be required, but it is often difficult to decide when this should be done. If the condition has been neglected or misdiagnosed, the destruction of the lining of the oesophagus and the surrounding fibrosis may be so severe that resection has to be carried out. For this reason, if a conservative or an expectant line of treatment is adopted in the early stages, a careful watch must be kept on the child and repeated *x*-ray examinations made so that any deterioration in the oesophageal condition can be dealt with at once. The management of these small patients sometimes presents very great difficulty.

Simple Strictures due to the Swallowing of Corrosives

The swallowing of corrosives, either accidentally or with suicidal intent, may result in the production of severe strictures, and recently there has been a tendency to treat these strictures by resection because of the supposed difficulty of carrying out dilatation effectively. The management of these strictures calls for painstaking care. After preliminary *x*-ray examination, oesophagoscopy is carried out, and it is sometimes found that an unsuspected foreign body lies above the stricture. Oesophagoscopic dilatation is seldom successful, because the interval between the dilatations is bound to be considerable, and the presence of the rigid instrument in the gullet interrupts normal peristaltic waves which help in the swallowing of the bougie. For these reasons "auto-dilatation" is to be preferred. The method is quite safe provided no force is used, and it is successful in nearly every case. When the stricture is so severe that a preliminary gastrostomy is called for the patient is encouraged to swallow a ureteric catheter, which is then recovered through

the gastrostomy opening and utilized as a guide for introducing a rubber tube and eventually a series of bougies of increasing size. By one or other of these methods dilatation has been successfully carried out in every case.

It is noteworthy that one patient, who had been burnt with nitric acid, had a fistula into the trachea and false passages in his oesophagus, the results of attempts at oesophagoscopic dilatation. Another patient, who had swallowed hydrochloric acid, had burnt the lower end of the oesophagus and also the pylorus, producing a stricture at each site. Yet another patient had had what appeared to be complete obliteration of his oesophagus for a period of 19 years. Patience is required in treating strictures of this nature by autodilatation, and the treatment must be continued for several years, but the final result should be a complete return to normal. Ten patients have been treated in this way in the past 20 years.

Congenital Atresia of the Oesophagus

It is very pleasant to finish my address by mentioning the great progress which has been made in the treatment of this anomaly. The condition was described by Gibson in 1697 and again by Sir Arthur Keith (1910) and others, but no patient was successfully operated upon until 1939, when a staged operation was carried out by Ladd (1944). The first completely successful operation of direct anastomosis was carried out in 1941 and reported by Haight and Towsley in 1943.

The commonest type of deformity is an atresia of the oesophagus at the level of the vena azygos arch, with the lower segment of the oesophagus arising from the trachea. This type of deformity accounts for 80% of the patients, and in most of the others there is an upper and lower blind segment without any communication with the trachea. It is difficult to estimate the frequency of this anomaly because even now many infants die from what is attributed to pulmonary or cerebral conditions and the true diagnosis is not suspected. Similarly death may be attributed to an imperforate anus when the real cause is an oesophageal anomaly.

FIG. 4.—Radiological appearance of congenital atresia of the oesophagus with fistula. The blind upper segment can be seen, and the fact that air is present in the stomach and intestines shows that there is a fistula between the lower segment and the trachea.

Cyanosis and attacks of choking in the newborn infant should at once suggest the possibility of an atresia of the oesophagus, and if a well-lubricated catheter, passed down the oesophagus via the mouth, is arrested at a point 10 cm. from the alveolar margin it is almost certain that the condition exists. The infant should then be transferred to a centre where *x*-ray confirmation and operation can be carried out (Fig. 4).

Both the operation and the anaesthesia require special experience and must be carried out very delicately. The subsequent nursing is of equal importance, and unless experienced and conscientious nursing is available it is useless to attempt the surgical treatment of these patients.

In my own first successful case the patient is now 7 years old, and altogether I have 17 patients who have recovered from the operation.

Conclusion

Many of the procedures in oesophageal surgery have now passed the pioneer stage and taken their place amongst the accepted operations. Some of them will always carry a very great risk, and for this reason it is essential that diagnosis should be accurate and that due consideration is given to the problem before embarking on this form of surgery. The treatment of cancer is still largely palliative but is none the less well worth while carrying out. Reflux oesophagitis presents a complex problem affecting patients of all ages. The symptoms may vary from a minor disturbance to a crippling or killing disease, and much work is needed to elucidate the underlying causes. The gastric secretion in infants requires further investigation and in adults there is scope for the simultaneous estimation of gastric and oesophageal pressures. The association of duodenal ulcer with reflux oesophagitis demands close study, always bearing in mind the possibility that in some patients at least the reflux oesophagitis appears to precede the formation of the hernia.

The problems connected with the diagnosis and treatment of oesophageal conditions require special methods and technique. This does not imply still narrower specialization, and in fact a broad approach is needed, because to understand and appreciate the various conditions affecting the oesophagus it is essential to have a knowledge of abdominal conditions in general and peptic ulceration and its complications in particular. Familiarity with the oesophagoscope and experience in paediatric surgery are also required. In fact the narrower the field the more general must be the approach.

REFERENCES

Allison, P. R. (1951). *Surg. Gynec. Obstet.*, **92**, 419.
—— and Borrie, J. (1949). *Brit. J. Surg.*, **37**, 1.
Barrett, N. R. (1950). Ibid., **38**, 175.
—— and Franklin, R. H. (1949). Ibid., **37**, 194.
Gibson, T. (1697). *The Anatomy of Humane Bodies Epitomized*, 5th edition. London.
Haight, C., and Towsley, H. A. (1943). *Surg. Gynec. Obstet.*, **76**, 672.
Keith, A. (1910). *British Medical Journal*, **1**, 301.
Kelly, A. B. (1930). *Proc. roy. Soc. Med.*, **23**, 1521.
Ladd, W. E. (1944). *New Engl. J. Med.*, **230**, 625.
Lewis, I. (1946). *Brit. J. Surg.*, **34**, 18.
Nissen, R. (1937). *Dtsch. Z. Chir.*, **249**, 311.
Ohsawa, T. (1933). *Arch. jap. Chir.*, **10**, 605.
Torek, F. (1913). *J. Amer. med. Ass.*, **60**, 1533.
Turner, G. G. (1933). *Lancet*, **2**, 1315.
Vinson, P. P. (1923). *Amer. J. Obstet. Gynec.*, **6**, 346.

AMYLOIDOSIS IN RHEUMATOID ARTHRITIS, AND SIGNIFICANCE OF "UNEXPLAINED" ALBUMINURIA

A REPORT OF EIGHT CASES

BY

GEORGE R. FEARNLEY, M.D., M.R.C.P.
Physician and Lecturer in Medicine

AND

RITA LACKNER, M.D., M.R.C.P.
Medical Registrar

Department of Medicine, Postgraduate Medical School of London, W.12

The complication of rheumatoid arthritis by amyloidosis is more often diagnosed by the pathologist than by the clinician. Fingerman and Andrus (1943) found amyloid deposition in 13 of 61 (21%) necropsied cases of rheumatoid arthritis. Teilum and Lindahl (1954) have reported an instance of 60%. By contrast, Hench and co-workers (1948) have stated that "the association of amyloidosis and rheumatoid arthritis rarely occurs, and then only in severe cases of long duration." On the clinical side, reports have been for the most part confined to single or at most two cases. The only clinical investigation of a population of rheumatoid arthritics for amyloidosis has been that of Unger *et al.* (1948),

who studied 52 rheumatoid patients by means of a modified Congo-red test, and found the complication to be present in six. Reece and Reynolds (1954) found five instances of amyloidosis with rheumatoid arthritis when all patients with the latter condition who attended their hospital from 1935 onwards were reviewed.

Our interest in the association of these two conditions was aroused when a patient with mild rheumatoid arthritis of about four years' duration died of renal failure. The ante-mortem diagnosis was chronic nephritis; at necropsy the cause of the renal failure was found to be amyloidosis, a possibility not entertained because the arthritis was so mild and of such short duration. We therefore decided to find out whether this complication could be recognized during life with greater certainty than previously. The initial problem was to find a clinical pointer. Splenomegaly and sometimes hepatomegaly occur not infrequently in uncomplicated rheumatoid arthritis and therefore cannot be taken to indicate the presence of amyloidosis. Since the essential morbidity of the complication is due to renal involvement, it seemed likely that the most reliable guide would be albuminuria. We therefore screened all patients with rheumatoid arthritis seen by us over a one-year period (July, 1953, to July, 1954) for albuminuria, and investigated its cause when found.

Clinical Material

A total of 183 cases, both in-patients and out-patients, were seen by us. Each of these patients had, in our opinion, unequivocal rheumatoid arthritis; patients whose diagnosis was doubtful were not included. Fig. 1 shows the age and sex distribution of the patients. Fig. 2 shows the duration of their rheumatoid arthritis. It can be seen that there was a fairly high proportion of patients whose disease was of short duration.

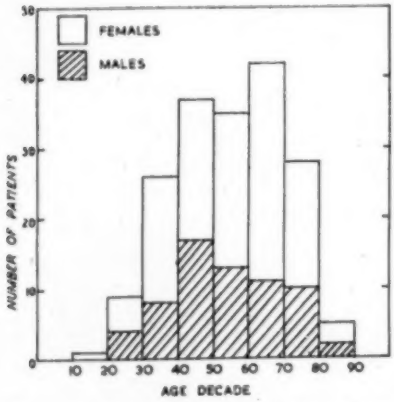


FIG. 1.—Age distribution of 183 patients with rheumatoid arthritis.

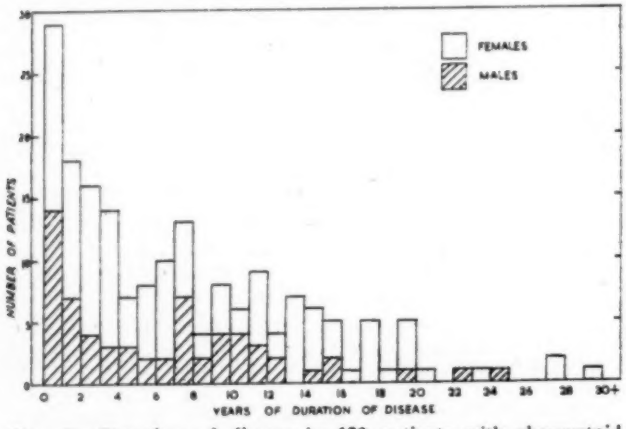


FIG. 2.—Duration of disease in 183 patients with rheumatoid arthritis.

Screening

The urine of out-patients was tested for albumin at each attendance; in-patients had the urine tested once or twice a week. The number of tests per patient varied from 1 to 25, depending on the number of out-patient attendances or the duration of stay in hospital, or a combination of both. A trace of albumin on only one occasion was disregarded. Those patients who showed a more persistent albuminuria were further investigated; a catheter or mid-stream specimen was taken and, where necessary, the appropriate urological investigation made. Of the 183 patients, 24 were found to have significant albuminuria: 5 of the 24 had urinary infection, 2 G.U. tuberculosis, 3 congestive heart failure, 1 chronic nephritis, 1 drug reaction, and 12 cases were unexplained. Of the latter 12 patients, one (F. P.) died of an acute surgical emergency before she could be further investigated, and at necropsy extensive amyloidosis with renal involvement was found. For various reasons it was not possible to investigate a further four of these patients. The seven remaining cases were investigated by the modified Congo-red test of Unger *et al.* (1948) or by liver biopsy, or by both methods.

Modified Congo-Red Test of Unger

Unger *et al.* have introduced a modification of the Congo-red absorption test, which we believe to be greatly superior to the test as usually performed. In brief, their modification consists in obtaining frequent samples during the first ten minutes after the injection of the dye, so that a zero time concentration can be obtained by extrapolation. The advantages over the standard Congo-red test in which a two- or four-minute sample is taken and the absorption calculated at one hour are as follows: errors due to incomplete mixing, which may take up to ten minutes or longer, are avoided; false-negative results due to very rapid fixation of the dye by massive amyloid deposits are also avoided. With the standard Congo-red test at least 90% absorption at one hour is required to constitute a positive result. Unger *et al.* believe that 35% or greater absorption at 30 minutes is good evidence of amyloidosis when their method is used: we have no reason to differ from their conclusion.

We modified the method slightly in that we set up a slow saline drip (10 drops a minute) which could be discontinued for the obtaining of blood samples, thus avoiding the discomfort to the patient of frequent venepunctures. Before each sample was obtained about 5 ml. of blood was aspirated and discarded in order to avoid error from saline dilution. Where necessary the volume of blood removed during the test was replaced by cross-matched bank blood.

Results

Fig. 3 shows the data obtained when the Congo-red test, as described above, was performed on three patients. The logarithm of Congo-red concentration is plotted against time, and then the theoretical zero time concentration is obtained by extrapolation from the readings made during the first 10 minutes after injection.

Patient A. H.—Rheumatoid arthritis with splenomegaly

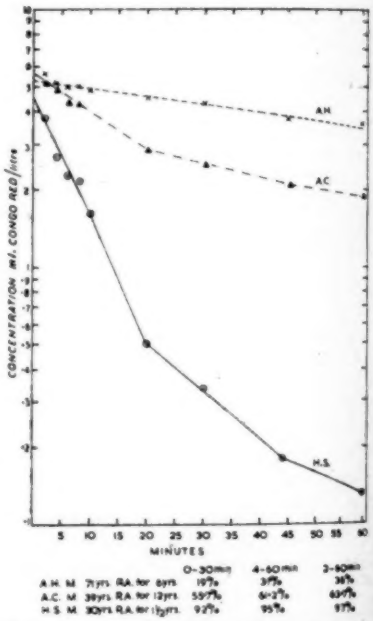


FIG. 3.—Congo-red absorption curves in three patients.

and hepatomegaly, but without albuminuria. The test was negative, there being only 19% absorption at 0–30 minutes. The test was also negative when the absorption at 60 minutes was calculated from the two-minute or four-minute sample (36% and 31% respectively), as is done with the standard Congo-red absorption test.

Patient A. C.—Rheumatoid arthritis with albuminuria. The test was positive, there being 55.7% absorption at 0–30 minutes. Note that when the absorption at 60 minutes was calculated from the two-minute or the four-minute sample, as in the standard test, the result was negative.

Patient H. S.—Rheumatoid arthritis, splenomegaly, hepatomegaly, and albuminuria. The test at 0–30 minutes was strongly positive (92%), as was also the absorption at 60 minutes calculated from either the two-minute or four-minute sample (97% and 95% respectively).

The table shows the data of the seven patients investigated and of the patient who showed amyloidosis at necropsy. Albuminuria was constant in every case except the latter, who showed only two positive tests out of five. The diagnosis was confirmed by liver biopsy in the first four patients

Case	Sex and Age	Duration	Liver	Spleen	No. of Urine Tests	Positive Albumin Tests	Congo Red 0–30 min. Absorption	Liver Biopsy
H. S.	M 30	1 yr.	+	+	25	25	92%	+
J. L.	M 74	8 ,,	+	0	10	10	90·9%	+
W. R.	F 38	16 ,,	+	0	12	12	77·9%	+
A. S.	F 61	11 ,,	+	0	13	13	53·5%	+
F. L.	F 67	18 ,,	0	+	13	12	Not done	+
A. C.	M 39	12 ,,	0	+	15	15	28·5% 55·7%	Not done
N. B.	M 55	15 ,,	0	+	3	3	77%	,, ,,
F. P.	F 69	18 ,,	+	0	5	2	P.m. confirmation extensive amyloidosis	

of the table. In Case F. L. severe flexion contractions of the elbows made it impracticable to perform the Congo-red test, and the diagnosis was made by liver biopsy alone. A liver biopsy was considered to be unnecessary for the next two patients. In Case A. C. the Congo-red test two months after the onset of albuminuria was negative. The albuminuria persisted, and when the test was repeated ten months later it had become positive with 55.7% absorption from

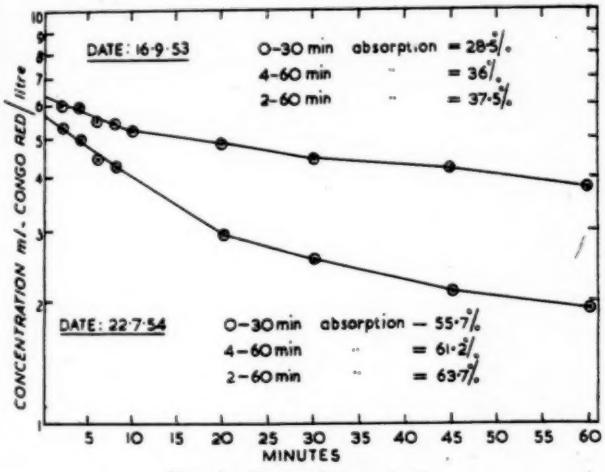

DATE: 16·9·53
0–30 min absorption = 28·5%
4–60 min " = 36%
2–60 min " = 37·5%
DATE: 22·7·54
0–30 min absorption — 55·7%
4–60 min " = 61·2%
2–60 min " = 63·7%
CONCENTRATION m/- CONGO RED/litre
MINUTES
5 10 15 20 25 30 35 40 45 50 55 60

FIG. 4.—Data of Case A. C.

0–30 minutes (see Fig. 4). In Case N. B., 77% absorption from 0–30 minutes was considered to be sufficiently good evidence of amyloidosis.

The duration of rheumatoid arthritis in these patients at the time the diagnosis of amyloidosis was made ranged from one to eighteen years, and six of the eight patients had had their disease for more than ten years. Both liver and spleen were palpably enlarged in only one patient, H.S. Hepatomegaly alone was present in four patients, and splenomegaly alone in three. This confirms that amyloidosis may be present without enlargement of both the liver and spleen, and, conversely, both these organs may be palpable when the quantitative Congo-red test is strictly negative (Case A. H., Fig. 3).

In two patients, H. S. and W. R., there was a past history of tuberculosis. Patient W. R. had had pulmonary tuberculosis some twenty years previously, complicated by tuberculous involvement of one knee-joint, for which arthrodesis had been performed. Her rheumatoid arthritis is relatively mild, and there is no evidence of active tuberculosis. Case H. S. is described briefly below.

This patient was aged 28 on his first admission to Hammersmith Hospital in July, 1952. In 1948 bilateral pulmonary tuberculosis had been diagnosed. Chemotherapy and a right pneumothorax failed to control the disease in the right lung, although the lesions in the left lung became inactive. In May, 1950, a right thoracoplasty was done, since when to the time of writing there has been no evidence of active tuberculosis. In July, 1952, he was admitted to Hammersmith Hospital with fever, tachycardia, and flitting polyarthritis, the onset of which was preceded by a sore throat three weeks before. A diagnosis of rheumatic fever was made, and sodium salicylate, 120 gr. (8 g.) a day, was given. At first his fever and joint symptoms responded, but, in spite of continued salicylate therapy, both fever and joint involvement reappeared a fortnight later. Gradually over the next three months the picture of rheumatoid arthritis appeared, with symmetrical involvement of hands, elbows, knees, and feet. Until May, 1953, the urine was free from albumin, and in that month albuminuria first appeared. Albuminuria (4–6 g. a day) then became persistent. In July, 1953, he was readmitted for further investigation. At that time the spleen but not the liver was palpably enlarged. Congo-red absorption and liver biopsy were as shown in the table. Subsequently the liver enlarged 6 in. (15 cm.) below the costal margin.

It should be noted that this patient had a past history of extensive tuberculosis, and it is entirely probable that this may have contributed to the development of amyloidosis. That the rheumatoid arthritis played a part, however, is indicated by the absence of the albuminuria until the arthritis had been present for a year, and by the subsequent rapid enlargement of the liver—all in the absence of any evidence of tuberculous reactivation.

Comment

Amyloidosis is one of the few potentially fatal complications of rheumatoid arthritis. Its recognition is therefore of some importance for prognosis. The finding of eight patients with this complication out of 183 patients with rheumatoid arthritis seen throughout a year suggests that amyloidosis in this disease is by no means rare. Since rheumatoid arthritis is extremely common, and since conditions which in the past produced amyloid deposition are now largely controlled by chemotherapy, it seems probable that rheumatoid arthritis may come to be the principal cause of amyloidosis. Missen and Taylor (1955), in a survey of necropsy material at the Postgraduate Medical School, found amyloidosis to be present in 8 of 48 patients with rheumatoid arthritis; each of these cases had shown proteinuria during life. We believe that attention to the presence of albumin in the urine of patients with rheumatoid arthritis would bring to light more of these cases.

Summary

Out of 183 patients with rheumatoid arthritis seen throughout a one-year period, eight were found to be suffering from amyloidosis.

The clinical pointer to the complication was albuminuria, unexplained by routine investigations.

The modified Congo-red test of Unger *et al.* was found to be more reliable than the standard Congo-red test in making the diagnosis.

In all patients the rheumatoid arthritis could be held responsible for the complication; in one, pre-existing tuberculosis may have played a part.

We wish to thank Dr. Sheila Sherlock and members of her firm for the liver biopsies; our colleagues, especially Dr. E. G. L. Bywaters, for permission to study their patients; and Miss Jeanette Pirkis for very efficient technical assistance and for drawing the illustrations.

REFERENCES

Fingerman, D. L., and Andrus, F. C. (1943). *Ann. rheum. Dis.*, **3**, 168.
Hench, P. S., and ten others (1948). *Ann. intern. Med.*, **28**, 66.
Missen, G. A. K., and Taylor, J. E. D. (1955). Unpublished data.
Reece, J. M., and Reynolds, T. B. (1954). *Amer. J. med. Sci.*, **228**, 554.
Teilum, G., and Lindahl, A. (1954). *Acta med. scand.*, **149**, 449.
Unger, P. N., Zuckerbrod, M., Beck, G. J., and Steele, J. M. (1948). *J. clin. Invest.*, **27**, 111.

MALARIAL THERAPY IN THE NEPHROTIC SYNDROME

BY

A. G. SHAPER, M.B., Ch.B., D.T.M.&H.

From the Tropical Diseases Centre, Sefton General Hospital, Liverpool

The effect of infection on the nephrotic syndrome has long been known, and massive diuresis with disappearance of oedema and great diminution in proteinuria has been observed to follow a variety of agents, including measles, chicken-pox, pneumonia, infusions of plasma or dextran, large doses of urea, or corticotrophin. The occasional dramatic response elicited by one or other of these agents has led several physicians to the use of malaria, as this was an acute fever that could be easily induced and readily controlled. The reasons for using malaria as a therapeutic agent have varied from that of Gairdner (1952), who considered that there was sufficient clinical evidence for the empirical use of acute febrile infections, to that of Byrne (1952), who holds that the response shown is due to stimulation of the acute defence phase of the adaptation syndrome of Selye. In conditions such as the nephrotic syndrome, where treatment after treatment may follow with no sign of symptomatic relief, "it behoves the physician to attempt in turn those agents which are known to have initiated remissions, as, in the earliest stages at least, this condition may be reversible" (Gairdner, 1952).

There is still much discussion and dispute regarding the nomenclature and classification of renal disease, and for the purpose of this report the term "nephrotic syndrome" is used. This term (Squire, 1953) is applied to those cases with oedema, proteinuria, and hypoalbuminaemia, but without hypertension, nitrogen retention, or electrolyte disorder, and without an appreciable excess of red blood cells in the urine. The majority of cases in this series can be regarded as Ellis Type II nephritis, but as this description implies the presence of particular pathological changes, and as in so many patients with renal disease the essential pathology is not known, it is justifiable to use a wider descriptive term.

Malarial therapy has been used over a period of several years in the Tropical Diseases Centre, using strains of benign tertian malaria, and occasionally *Plasmodium ovale*, in patients with the nephrotic syndrome. In some it was used as a primary procedure, in others as a last resort after many varied and unsuccessful forms of therapy. Brief clinical reports are given of seven patients in whom the infection had been sufficiently severe and long-continued to regard them as having undergone "malarial therapy." The methods of infection and the management of induced malaria are dealt with by Shute (1952).

Method

Selection of Cases.—There are no precise indications for the use of malarial therapy. It is usually reserved for patients with a nephrotic syndrome which has failed to respond to more conservative forms of treatment.

Duration of Treatment.—The patient should be allowed to have as many rigors as he is capable of withstanding. The indications for cutting short the treatment are a marked deterioration in general condition, sustained fever, or severe oliguria.

Interruption of Quotidian Fever.—In most cases the fever initially assumes a quotidian periodicity but then settles down to a tertian periodicity. In some the quotidian fever persists, and in order to procure relief from the daily paroxysm a single dose of bismuth sodium thioglycollate ("thio-bismol"), 0.2 g. intramuscularly, may be given. This will usually cause the fever to become tertian in periodicity. Alternatively, small doses of quinine may be given for one day. This may stop the fever, but it will relapse in a week or two.

Method of Eradication of Malarial Infection.—In all patients the fever can rapidly be terminated by giving full doses of chloroquine, mepacrine, or quinine for a few days. In those infected by blood inoculation from other patients suffering from malaria this will eradicate the infection. In patients infected by parenteral injection of sporozoites, or by feeding infected anopheline mosquitoes, the treatment must be continued with a ten-day course of pamaquin, 10 mg. three times a day (Adams and Maegraith, 1953), to sterilize the exo-erythrocytic cycle of parasite development which results from this mode of infection, or a relapse will occur.

Case 1

The patient, a man aged 29, had a history of oedema of the lower limbs and puffiness of the face, associated with some lumbar backache over a period of six weeks. On admission there was pitting oedema of the lower limbs of moderate severity and the urine contained a moderate amount of protein, granular casts, and a few red blood cells. The blood pressure was 130/80 mm. Hg; the retinal vessels were normal. Other findings were: haemoglobin, 100%; serum proteins, 2.45 g.%, with reversal of the albumin/globulin ratio; blood urea, 28 mg. per 100 ml. and serum cholesterol, 262 mg. per 100 ml. The patient was observed for three months, during which time he was treated with a high-protein salt-free diet; although the serum protein level rose to 5.67 g.% the oedema gradually increased in severity until it was generalized and extreme.

Malarial Therapy.—He was infected with a strain of *P. vivax*, using infected anopheline mosquitoes. After a short initial period of irregular fever the temperature assumed the usual tertian periodicity. After four pyrexial episodes associated with severe rigors, his oedema had further increased, so that even in the sitting position it extended to his cervical region. There was a marked reduction in urinary output, accompanied by gross haematuria. The fever was stopped with chloroquine.

Four days after the subsidence of fever his urinary output increased to 80–100 fl. oz. (2,270–2,840 ml.) daily, on an intake of 40–50 fl. oz. (1,140–1,420 ml.). This diuresis continued for four weeks, leaving only minor residual oedema of the legs and sacrum. The diuresis then ceased, and over the next two weeks there was a slight increase in the oedema. As a relapse had not occurred the patient was reinfected with benign tertian malaria, and developed a gross haematuria, followed after 24 hours by a temperature rise and a rigor. After four pyrexial episodes, the haematuria was still present and the oedema was more marked. The fever was interrupted for one week with bismuth sodium thioglycollate, and its reappearance was again preceded by gross haematuria, followed by increasing oedema. After a further five pyrexial episodes the fever was arrested with chloroquine. During the next eleven days

there was a moderate diuresis, the urinary output exceeding fluid intake by an average of 10 fl. oz. (284 ml.) daily. At this stage the general condition was very good, there was minimal oedema of the ankles on walking, and the urine showed a trace of protein but no blood or casts.

Frequent estimations of the blood urea during the course of the malaria showed fluctuations up to 50 mg. per 100 ml. The serum protein fell to 3.77 g.% in the first week of fever, rising after two weeks to 5.02 g.% and falling to 4.7 g.% at the termination of the infection six weeks after commencement. There was constant reversal of the A/G ratio.

Six months later the patient was readmitted, having suffered a relapse of his initial sporozoite infection. This had again been heralded by haematuria, followed two days later by fever. In the interim he had remained extremely well, with only slight swelling of the ankles on moderate exercise—for example, dancing. On examination he had no oedema, and his blood pressure was 110/65 mm. Hg. The serum proteins were 6.79 g.% (albumin 2.54 g., globulin 4.25 g.), and the blood urea 25 mg. per 100 ml.; the urine contained a moderate amount of protein, a few granular casts, and a small number of red blood cells. During the ten days over which the patient was observed during treatment with quinine and pamaquin his urinary output exceeded his intake by an average of 19 fl. oz. (540 ml.) daily.

Subsequent History.—Eighteen months after the start of malarial treatment the patient remained well and was carrying on his employment as a travelling salesman. He felt tired occasionally, but had no swelling of the legs even on continued exercise. There was no sacral or limb oedema, the fundi were normal, and the blood pressure was 130/90 mm. Hg. The urine contained a small amount of protein, a few granular casts, and some red blood cells. The serum proteins were 7.1 g.% (albumin 4.04 g., globulin 3.06 g.); serum cholesterol, 274 mg. per 100 ml.; and blood urea, 25 mg. per 100 ml.

Case 2

The patient, a man aged 47, had suffered from swelling of the lower limbs, which slowly increased over the 20 months prior to his admission. On admission there was marked pitting oedema of the lower limbs, scrotum, and sacrum, with ascites and oedema of the lower abdominal wall. The blood pressure was 180/95 mm. Hg; blood urea 54 mg. per 100 ml.; and serum cholesterol, 199 mg. per 100 ml.; the urine contained a trace of protein, with granular casts and a few red blood cells. Abdominal paracentesis was done on several occasions.

Malarial Therapy.—The patient was infected intravenously with sporozoites of benign tertian malaria, and became febrile after 12 days; he subsequently had eight severe paroxysms with rigors. During this period his oedema and ascites increased, his haemoglobin level dropped from 85% to 37%, and there was a marked reduction in his urinary output. The blood urea rose to 60 mg. per 100 ml., and on account of his poor general condition the malaria was stopped with chloroquine. The plasma proteins after malaria therapy were 4 g.% (albumin 2.53 g., globulin 1.47 g.). In the next four weeks no diuresis occurred and abdominal paracentesis had to be repeated on several occasions. The patient returned home and remained in bed, taking a self-prescribed remedy of lemon-juice, tartaric acid, and magnesium sulphate. After three weeks at home he noticed an obvious increase in his daily urinary output, and one week later his sporozoite-induced malaria relapsed. He continued to have paroxysms for three weeks before he returned to hospital. He then had no ascites or oedema of the abdominal wall, and there was only minimal pitting oedema of the lower limbs. After two further rigors in hospital the malarial infection was eradicated with a course of quinine and pamaquin. The blood pressure was 130/80 mm. Hg; blood urea, 60 mg. per 100 ml.; and the urine showed a heavy albumin deposit, with granular casts and occasional red blood cells. No estimation of serum proteins was made.

Subsequent History.—One year later he was back at work as a lorry driver. He had had no swelling of his legs, but there was slight breathlessness on exertion. There was no anaemia or oedema of his lower limbs, and his fundi were normal. The blood pressure was 180/100 mm. Hg, and the urine contained a large amount of protein but no casts or blood cells. Serum proteins were 5.4 g.% (albumin 4.2 g., globulin 1.2 g.); serum cholesterol, 187 mg. per 100 ml.; and blood urea, 138 mg. per 100 ml.

Case 3

A man aged 52 complained of increasing swelling of the lower limbs, puffiness of the face, and dyspnoea on exertion over the two months prior to admission. On admission there was moderately severe oedema of the lower limbs and sacrum, the blood pressure was 160/95 mm. Hg and the urine contained protein and hyaline and granular casts. The serum proteins were 4.56 g.%, with a reversed A/G ratio; blood urea, 32 mg. per 100 ml. and serum cholesterol, 250 mg. per 100 ml.

Malarial Therapy.—The patient was infected with benign tertian malaria by intravenous blood inoculation; after seven days his temperature rose sharply, and he had malarial paroxysms on 14 successive days. A small dose of quinine was given, and this produced an apyrexial period of seven days, which was followed by a further five rigors before the malaria was arrested therapeutically. Over this period the haemoglobin dropped from 85% to 30%, the blood urea rose to 54 mg. per 100 ml., and the serum proteins fell to 4.04 g.% (albumin 1.41 g., globulin 2.63 g.).

During the 24 days of malarial treatment the urinary output varied from 20 to 50 fl. oz. (570 to 1,420 ml.), but at no time did the output exceed the fluid intake. Two days after the malaria had been treated a diuresis began; this persisted for three weeks, during which the patient remained in hospital. The average daily excess of output over intake was 20 fl. oz. (570 ml.), no allowance being made in this calculation for the fluid loss via skin, respiration, and stools. On discharge the patient still had a moderate degree of pitting oedema of the lower limbs, but the diuresis did not seem to be diminishing. The urine still contained protein and casts.

Subsequent History.—For one year after discharge he led a sedentary life and had not returned to work. He remained dyspnoeic on exertion, and noticed slight swelling of his ankles on moderate exercise, but there had been no marked oedema. On examination his general condition was good, but there was a small left pleural effusion. His blood pressure was 200/120 mm. Hg; blood urea, 64 mg. per 100 ml.; serum cholesterol, 350 mg. per 100 ml.; and serum proteins, 5.21 g.% (albumin 2.9 g., globulin 2.31 g.). The urine contained a moderate amount of protein, granular and epithelial casts, and a few red blood cells.

Case 4

This patient, a youth of 18, was admitted three months after the gradual onset of swelling of the legs and face, associated with a feeling of tiredness. He had been treated with antibiotics, mersalyl, ion-exchange resins, and dietary measures, all without success. On admission there was marked ascites with oedema of the lower limbs, sacrum, genitalia, and arms, and in addition there were bilateral pleural effusions. The blood pressure was 135/90 mm. Hg; serum proteins, 4.18 g.% (albumin 1.11 g., globulin 3.07 g.); serum cholesterol, 395 mg. per 100 ml.; and blood urea 68 mg. per 100 ml. The urine contained protein, many granular casts, a few hyaline casts, and a few red blood cells.

Malarial Therapy.—He was infected with *P. vivax* by intravenous blood inoculation, and within a period of four days (April 26) developed gross haematuria, followed by pyrexia, and a sudden increase in the oedema. He then suffered nine malarial paroxysms, and during this period showed no tendency to diuresis. His urinary output fell

gradually to about 15 fl. oz. (420 ml.) daily, his haemoglobin dropped from 80% to 30%, and there was a marked deterioration in his general condition. The malaria was interrupted by subcurative quinine treatment (May 11), and an abdominal paracentesis relieved his distress. Twelve days (May 23) later fever recommenced, and he suffered a further nine paroxysms. There was no diuresis during this time, and further abdominal paracentesis was required. The malarial infection was then eradicated with chloroquine (June 4). During the next three months no diuresis occurred. Details of the blood chemistry are set out in the Table.

Blood Chemistry at Intervals During the Malarial Fever in Case 4

	April 29	May 4	May 9	May 14	May 24	June 1	July 31
Total protein (g.%)	4·91	4·46	3·79	4·30	3·46	3·26	2·96
Albumin (g.%) ..	1·61	2·24	1·46	1·63	1·45	1·41	1·52
Globulin (g.%) ..	3·92	2·22	2·46	2·67	2·01	1·85	1·44
Blood urea (mg. per 100 ml.) ..	80	68	60	61	46	53	51
Cholesterol (mg. per 100 ml.) ..							543

Subsequent History.—Over a period of four months following malarial therapy he remained on a high-protein diet with gradual decrease in the oedema. He has been discharged from hospital with pitting oedema of a moderate degree.

Case 5

A woman aged 25 had noticed a gradual swelling of the lower limbs, with progressive increase in weight over a period of eight months. On admission she had gross oedema of the lower limbs and thighs. The blood pressure was 140/95 mm. Hg, and the urine contained protein, granular casts, and an occasional red blood corpuscle. The blood urea was 32 mg. per 100 ml.; cholesterol, 696 mg. per 100 ml.; and total serum proteins 5.01 g.%.

Malarial Therapy.—The patient was infected by blood inoculation with benign tertian malaria, and after ten days' incubation had nine paroxysms. There was marked constitutional upset with an increase in the proteinuria and she became very distressed. The malarial infection was stopped. She was observed for a further two months, during which time there was no diuresis or improvement in her clinical condition. At this stage the serum proteins were 4.9 g.%, the blood urea was 27 mg. per 100 ml., and the serum cholesterol had dropped to 350 mg. per 100 ml. Two months later the oedema had increased considerably, and the serum cholesterol had risen to 530 mg. per 100 ml. The patient has been watched for a further two years; although there has been a gradual improvement in her physical condition, she still has protein and casts in the urine. Her blood pressure has remained at normal levels, and she has slight oedema on exercise only.

Case 6

The patient, a woman aged 52, was admitted with oedema of the lower limbs, abdominal wall, and arms, and some puffiness of the face of two weeks' duration. There had been no preceding acute infection, and she was considered to be suffering from an exacerbation of a latent nephritis. On admission she had bilateral pleural effusions, the blood pressure was 180/100 mm. Hg, and the urine contained protein, granular casts, and a few red blood cells. The serum proteins were 4.56 g.%; blood urea, 50 mg. per 100 ml.; and serum cholesterol 127 mg. per 100 ml. There was no response to infusions of dextran or to high-protein salt-free diet.

Malarial Therapy.—The patient was infected with benign tertian malaria by intravenous blood inoculation, and became pyrexial after two weeks; she was allowed to have five paroxysms of fever. She was very exhausted and cyanosed during each attack, so the fever was discontinued by chloroquine treatment. Four days later there was a slight increase in the urinary output, but this moderate diuresis was sustained for only 48 hours, and it made no clinical difference to her oedema. Her condition one month after malarial therapy was slightly worse than initially, her protein level was 5.46 g.%, and her blood urea was 52 mg. per 100 ml. Two months later she died from pulmonary oedema and generalized oedema due to chronic nephritis.

Case 7

A woman aged 22 had suffered a gradual onset of generalized oedema, thought to be due to Ellis Type II nephritis, for which she had been treated for nine months. On admission she had marked oedema of the lower limbs, gross ascites and oedema of the abdominal wall, and a large right pleural effusion. The blood pressure was 120/90 mm. Hg, the urine contained protein, granular and epithelial casts, and red blood cells. The blood urea was 34 mg. per 100 ml. and the serum cholesterol 214 mg. per 100 ml. She was observed for a further four months on various treatments, during which time there was a gradual deterioration in her condition, with increase in the oedema.

Malarial Therapy.—The patient was infected by blood inoculation with *P. ovale*, and after eight days she became pyrexial. There was a sudden and marked increase in the amount of oedema and ascites, and she thereafter suffered seven very mild paroxysms, with only minor fever, and at times no rigors. At no period did she show any clinical signs of improvement in her renal condition, and there was no diuresis. Her haemoglobin fell from 80% to 50%, her blood urea rose to 52 mg. per 100 ml., and repeated abdominal paracenteses were necessary. The malaria remitted spontaneously at this stage, and she remained apyrexial for two weeks. She then relapsed, but, apart from two or three minor pyrexial episodes, the presence of malaria parasites in the blood was not associated with any marked constitutional effects. The infection was eradicated with proguanil. One month later her condition was still unchanged, so she was reinfected, this time with benign tertian malaria by intravenous blood inoculation. After two minor pyrexial episodes her physical condition began to deteriorate rapidly, so the infection was stopped. Two weeks later she died.

Comment

Of these seven nephrotic patients treated by malarial infection three have had a marked remission of symptoms. Case 1 showed a most dramatic response, which has been well sustained. Cases 2 and 3 have been free of symptoms for a year, and the former, despite a high blood urea level, is working full time and feels well. The improvement shown in Case 4 cannot be closely associated with the malarial therapy—it is probably due to the high-protein diet—while the improvement in Case 5 cannot be associated with malarial therapy. The last two patients (Cases 6 and 7) died of their basic condition, but as they were both severely ill and the malarial paroxysms were poor or curtailed in number it would be unfair to say that malarial therapy had failed. Since the aetiology of the renal condition in these seven patients is not known, one can but speculate on the mechanisms by which the improvement has been initiated in Cases 1, 2, and 3. These cases do, however, encourage the continued trial of malarial therapy in this type of renal disease.

In Cases 1 and 4 the onset of malarial fever was preceded by macroscopic haematuria; this may have been an indication of increased damage to the renal tissues. In malaria the serum proteins, particularly the serum albumin, are usually reduced and there may be considerable increase in the serum globulin. Blood urea levels were not raised to any significant extent, despite pre-existing renal damage. The behaviour of serum cholesterol is extremely important, as it has been postulated by Gairdner that the beneficial effects of malarial therapy may be due to reduction in the serum cholesterol level. Most workers have reported a reduction in the cholesterol concentration at some time during the course of the malarial attack. Crespin and Zaky (1919) showed that the level fell to below normal values

just before the onset of a paroxysm, became normal or slightly raised in the pyrexial period, and fell to normal in the latent periods between attacks. Fairley and Bromfield (1933) in cases of induced malaria, showed that although hypocholesterolaemia occurred in some cases of well-established malaria, the levels rose to normal upon the termination of the attack.

A point in assessing the effects of malarial therapy is to preclude any diuretic action on the part of the drugs used to terminate or eradicate the infection. To this end fluid-balance charts were examined from 20 National Service men admitted to the Tropical Diseases Centre suffering from acute benign tertian malaria. They were all treated with chloroquine, quinine, and pamaquin; in none of them was any significant or prolonged diuresis noted as a consequence. It was therefore concluded that if a diuresis did occur following the use of antimalarial drugs in patients with the nephrotic syndrome it was in no way related to the action of these drugs.

Summary

Seven cases of the "nephrotic syndrome" have been treated by malarial therapy.

Three cases have had marked remission of symptoms lasting over one year.

It is considered that there is an indication for the continued use of malarial treatment in nephrotic patients who do not respond to more conservative treatment.

I wish to thank Dr. A. R. D. Adams, Professor B. G. Maegraith, and Dr. C. S. McKendrick, under whose care these patients were admitted. I am grateful to Dr. A. R. D. Adams for his advice and assistance in preparing this paper.

References

Adams, A. R. D., and Maegraith, B. G. (1953). *Clinical Tropical Diseases*. Blackwell Scientific Publ., Oxford.
Byrne, E. A. J. (1952). *Lancet*, **1**, 844.
Crespin, J. C., and Zaky, A. (1919). *C.R. Soc. Biol. (Paris)*, **82**, 216.
Fairley, N. H., and Bromfield, R. J. (1933). *Trans. roy. Soc. trop. Med. Hyg.*, **27**, 289.
Gairdner, D. (1952). *Lancet*, **1**, 842.
Shute, P. G. (1952). Ibid., **2**, 333.
Squire, J. R. (1953). *British Medical Journal*, **2**, 1389.

Medical Memoranda

A Fatal Case of Pernicious Anaemia Associated with Chloramphenicol Treatment

An increasing number of deaths from aplastic anaemia after treatment with chloramphenicol are being reported. A case of pernicious anaemia is described below which, on account of numerous intercurrent infections, was treated with two courses of chloramphenicol. Subsequently the patient developed an aplastic anaemia and died five months after the second course.

Case History

A married woman aged 65 was admitted to hospital on August 1, 1952, with a six-months history of dyspnoea on exertion, swelling of the ankles, and increasing pallor.

On examination there was extreme pallor with a lemon-yellow tint. The tongue was smooth and she had a pyrexia of 99 to 100° F. (37.2 to 37.8° C.). There were signs of congestive cardiac failure, with normal heart sounds, and a blood pressure of 130/50 mm. Hg. No abnormalities were found in the chest, abdomen, or central nervous system. A catheter specimen of urine showed a heavy pyuria with a growth of *Bact. coli* organisms. A blood count gave: Hb, 2.5 g.% (14.8 g.=100%); red cells, 570,000 per c.mm.; C.I., 1.5; M.C.V., 123 cubic μ; M.C.H.C., 35.7%; white cells, 4,950 per c.mm. (polymorphs 57%, lymphocytes 43%). Nucleated red cells were seen in the peripheral blood films. The serum bilirubin was 0.9 mg. per 100 ml. Histamine-fast achlorhydria was present. Iliac bone puncture revealed a megaloblastic marrow. A diagnosis of pernicious anaemia was made on the above findings.

After an initial transfusion of ½ pint (280 ml.) of packed red cells, treatment with vitamin B_{12} was begun on August 5. For the first fortnight she was given 100 μg. weekly, and thereafter until she left hospital on September 10 she had 100 μg. fortnightly. A maximum reticulocyte response of 11% occurred five days after the onset of specific treatment. Although the response seemed a low one in view of the initial red cell count, it is known that intercurrent infections will considerably modify the reticulocyte peak, and at this stage the patient had a heavy urinary infection. Furthermore, a reticulocyte crisis may be reduced if specific treatment is preceded, as in this case, by a blood transfusion. The blood count on August 23 was: Hb, 6.5 g.%; red cells, 2,220,000 per c.mm.; C.I., 1. On August 25 it was: Hb, 10.7 g.%; red cells, 3,820,000 per c.mm.; C.I., 0.9; white cells, 22,400 per c.mm. (polymorphs 82%). By September 16, when she left hospital, the blood count was: Hb, 11.7 g.%; red cells, 4,100,000 per c.mm.; C.I., 0.96.

In the meantime, starting on August 3, a five-day course of "sulphatriad" (8 g.) was given for the urinary infection. By August 9 the urine was sterile. On the 10th a ten-day course of 19 g. of chloramphenicol was started on account of a left basal pneumonia. By the end of August frequency and dysuria had returned, and a further catheter specimen on September 8 showed a heavy growth of *Bact. coli*, which *in vitro* tests showed to be sensitive only to chloramphenicol. A further course of 9 g. of this drug was therefore given between September 10 and 15. The urine again became sterile, but before leaving hospital a further reinfection with *Bact. coli* was treated with 12 g. of chlortetracycline. During all this time the blood urea was never higher than 50 mg. per 100 ml.

On September 16 the patient left hospital symptom-free on a maintenance dose of 100 μg. of vitamin B_{12} fortnightly. She was next seen on November 28, when the blood count was: Hb, 6.5 g.%; red cells, 2,360,000 per c.mm.; C.I., 0.90. At this stage the amount of vitamin B_{12} was increased to 100 μg. twice weekly. A fortnight later the blood count was approximately unchanged, but by December 19 it had fallen to: Hb, 5.6 g.%; red cells, 2,100,000 per c.mm.; platelets, 62,000 per c.mm. She had had numerous epistaxes during the previous three weeks.

She was readmitted on December 20 and given a small blood transfusion. Also liver treatment consisting of "hepastab," 2 ml. on alternate days, was started. On January 2, 1953, a blood count showed Hb, 6.8 g.%; red cells, 2,350,000 per c.mm.; C.I., 1; white cells, 2,600 per c.mm. (polymorphs 37%, lymphocytes 63%). On the same day an iliac puncture suggested an aplastic anaemia. The total nucleated count was 7,600 per c.mm. and myeloid hypoplasia together with a relative erythroid hyperplasia was present, giving a total myeloid–erythroid ratio of 2:1 respectively. Ten days later, in spite of a further transfusion, the blood count was Hb, 7.04 g.%; red cells, 2,270,000 per c.mm.; C.I., 1; platelets, 41,000 per c.mm. Thereafter she developed numerous petechial haemorrhages and died on February 19.

Necropsy.—The body was that of a thin woman with numerous petechial haemorrhages in the skin and subcutaneous tissue. The lungs were pale but otherwise normal. The myocardium showed fatty degeneration and numerous haemorrhages. The gastro-intestinal mucous membrane was congested and haemorrhagic, the stomach otherwise appearing normal. The liver showed fatty degeneration, and the spleen numerous old infarctions. The kidneys showed bilateral arteriosclerosis with disruption of the renal pattern. The ureters and bladder were normal. The bone marrow of the sternum and iliac bones and femur were pale and fatty. The pancreas and adrenals appeared normal.

Histology.—There was fatty degeneration of the liver, and the splenic pulp showed poorly defined Malpighian

corpuscles and excess of reticulum cells. Bone-marrow sections cut from the ilium showed hypoplasia affecting granulopoiesis more than erythropoiesis. The number of mature granulocytes was greatly reduced and very few megakaryocytes were seen. The number of reticulum cells was increased. The lymphocytes appeared to be normal. As regards the red-cell series, there seemed to be a maturation defect at the normoblast stage.

COMMENT

It is known that untreated cases of pernicious anaemia may terminate spontaneously in aplastic anaemia. Blackburn *et al.* (1952) recommended a maintenance dose of at least 50 μg. of vitamin B_{12} a fortnight for patients with pernicious anaemia uncomplicated by neurological involvement. In the above case the maintenance dose was never less than 100 μg. fortnightly.

Sulphonamides are occasionally responsible for the development of aplastic anaemia (Strauss, 1943). Usually only the white-cell series is affected, and granulopenia develops within a month. However, in the above case the white cells numbered 22,400 per c.mm. (polymorphs 81%) seven weeks after the end of the sulphonamide course, and three weeks later, when the patient left hospital, there was still no evidence of aplastic anaemia. Nevertheless, as Hodgkinson (1954) states, sulphonamides may have an additive effect in cases of aplastic anaemia primarily due to chloramphenicol.

In the above case two courses of chloramphenicol of 19 and 9 g. respectively were given. Judged by the standards of Hodgkinson (1954) the dosage of the individual courses was not heavy, although the total dosage was high.

In conclusion it is submitted that any drug that is known to be able to cause marrow aplasia, such as chloramphenicol, should be used with the greatest caution, if at all, in pernicious anaemia. In this respect Witts (1941) reported a relapse in a case of pernicious anaemia, after a good response to treatment, upon the administration of "allonal." The latter contains amidopyrine, which, like chloramphenicol, belongs to the benzamine group of drugs. It is probable that similar care should be taken in using chloramphenicol in other blood diseases in which the bone marrow already shows a disturbance of its normal function and appearance.

I am indebted to Dr. J. H. Cobb, of the Royal Surrey County Hospital, Guildford, for permission to publish this case. I wish to thank Dr. S. Keys for his reports on the pathological investigations.

M. A. PEYMAN, B.M., M.R.C.P.

REFERENCES

Blackburn, E. K., Burke, J., Roseman, C., and Wayne, E. J. (1952). *British Medical Journal*, **2**, 245.
Hodgkinson, R. (1954). *Lancet*, **1**, 285.
Strauss, A. M. (1943). *Amer. J. clin. Path.*, **13**, 249.
Witts, L. J. (1941). *British Medical Journal*, **2**, 199.

Accidental Poisoning with Tetrachlorethane

Three cases of accidental poisoning with tetrachlorethane are reported, it having been given in mistake for tetrachlorethylene.

Normally, owing to its cheapness, I treat cases of hookworm disease with carbon tetrachloride, but in children and adults who are underweight tetrachlorethylene is given owing to less risk of toxic effects.

CASE REPORTS

Ancylostoma duodenale ova were isolated from the faeces of all three patients, who were admitted for starvation followed by tetrachlorethylene. The patients were a young African man, weight 102 lb. (46.3 kg.), a young African woman, weight 108 lb. (49 kg.), and an African girl aged about 12 years, weight 60 lb. (27.2 kg.). The doses of tetrachlorethylene were 3 ml., 3 ml., and 2 ml. respectively, and were given at 7.15 a.m. An hour and a half later an orderly noticed that the man appeared to be sleeping, and that he could not be roused. Shortly afterwards a nurse reported that the woman was in exactly the same state.

On examination the man was deeply unconscious and both corneal and pupil reflexes were absent; the pupils were moderately contracted. The limbs were flaccid and the breathing was shallow; the respiratory rate was 12 a minute. Gastric lavage was started immediately and 20 mg. of amphetamine sulphate was left in the stomach. The pulse rate was 90 and the volume poor; blood pressure 60/46 mm. Hg. Nikethamide, 5 ml., was injected intravenously, following which the systolic pressure rose to over 80 and the breathing improved.

The woman was also deeply unconscious, and the findings were essentially the same as in the man; she was treated in a similar way. Meanwhile the child, who seemed unaffected, was given a strong emetic with very good effect, for she did not lose consciousness or suffer any other ill effect.

During the course of the next two hours a close watch was kept on them, and the adults each had to have further doses of nikethamide owing to the falling blood pressure and reduced respiratory excursions. However, the depth of unconsciousness became less and both were able to respond to the spoken word at about 11.15 a.m.—that is, some four hours after the administration of the doses. They seemed euphoric for a few hours but suffered no harm from their experience; however, as a precaution they were kept in hospital for a week on high glucose intake, "casilan," and injections of crude liver extract and vitamin B complex.

A month later the man could not be traced as he had been discharged from his work, but the other two were in excellent health, and microscopical examination revealed that there were no ova in the stools.

At the first indication of trouble I sent for the bottle, which was a new one and seemed to be in order, but it was only when I mentally spelt the word that I saw it was *tetrachlorethanum* and not *tetrachlorethylene* which had been requested from the suppliers.

COMMENT

Tetrachlorethane is a colourless liquid with an odour resembling carbon tetrachloride. It is used in many industrial processes as a solvent for cellulose acetate and nitrate, bitumin, waxes, resins, pitch, tar, sulphur, rubber, and oils. It is the most toxic of the chlorinated hydrocarbons, exerting a narcotic effect and causing profound metabolic injury, especially liver atrophy. It has been the cause of many cases of poisoning when its vapour has been inhaled; in 1914 and 1915 there were at least 70 cases of jaundice, with 12 deaths, among workers using aeroplane "dope" (Willcox *et al.*, 1915).

Only two cases of poisoning following its ingestion have been reported (Hepple, 1927; Elliott, 1933). Both these men became deeply unconscious and cyanosed with loss of reflexes and died. Post-mortem findings were chiefly of congestion of the respiratory and gastric mucosae, although one case also showed marked cloudy swelling of the cells of the liver and convoluted tubules of the kidney.

In Hepple's case 12 ml. was distilled from the stomach contents after death, so the amount must have been much greater, as gastric lavage had been performed. It must have considerably exceeded the lethal dose, which cannot be very much more than 3 ml. Gastric lavage should be thorough and persistent, as tetrachlorethane has a higher specific gravity than water and is not miscible with it, and so may defy efforts to remove it.

J. M. WARD, M.R.C.S.,
Que Que, Southern Rhodesia.

REFERENCES

Elliott, J. M. (1933). *J. roy. Army med. Cps*, **60**, 373.
Hepple, R. A. (1927). Ibid., **49**, 442.
Willcox, W. H., Spilsbury, B. H., and Legge, T. M. (1915). *Trans. med. Soc. Lond.*, **38**, 129, 139, 144.

Reviews

MEDICAL EDUCATION IN BRITAIN AND THE U.S.A.

Medical Students and Medical Sciences: Some Problems of Education in Britain and the United States. By D. C. Sinclair, M.A., M.D. (Pp. 154+x. 25s.) London, New York, Toronto: Oxford University Press. 1955.

Dr. Sinclair, who has frequently published articles on medical education in this country and in America, has had the advantage of a Rockefeller Foundation grant enabling him to spend three months in the U.S.A., where he made a study of education in the "medical sciences." This has allowed him to produce an admirable book concerning medical education in Britain and the United States, the two countries in which the subject can be said to be most advanced. He draws a lively contrast between the requirements and the practices of the two countries, and shrewdly analyses the approach of each towards its own particular problems, which, indeed, are not identical.

The title "Medical Sciences" restricts the author, by his own definition, to what is often referred to as the pre-clinical stage of medical education—namely, anatomy, physiology, biochemistry, pharmacology, pathology, bacteriology, and a number of other subjects which vary from one school to another. The book, in four sections, deals with the student himself, his selection, and his problems in general; with the teacher (as distinct from the research worker), his teaching, and the methods for assessing the knowledge of the teacher's pupils; with the material which is taught; and with present-day educational experiments. One is left with the impression that the author believes that the present curriculum for the medical sciences has no glaring faults when presented by competent teachers, but that it could with advantage be reasonably pruned of late nineteenth and early twentieth century shibboleths and be (sacred word) "integrated" for the benefit of the student. It is easier to advocate this than to effect it, since heads of departments are often allergic even to the idea, and how much more to its execution. One has to admit, also, that whatever reforms are made in individual schools must necessarily be uncontrolled experiments, even as the "vertical teaching" at Western Reserve University must be so regarded.

This book can be read with considerable profit, much enjoyment, and with many a quiet chuckle, since the author has an attractive style, a dry, even pungent wit, a gift of phrase, and an aptitude for making his points. It can be commended to all, but especially to those who feel that medical education is a dull subject or one which can look after itself.

LIONEL WHITBY.

OBSTETRIC PROBLEMS

Practical Obstetric Problems. By Ian Donald, M.B.E., M.D., B.S., B.A., M.R.C.S., L.R.C.P., M.R.C.O.G. (Pp. 578; illustrated. 45s.) London: Lloyd-Luke (Medical Books) Ltd. 1955.

The author's warning (or promise) that his natural exuberance may bubble into the text, and the dust-cover comment that there should be no place for dullness in textbooks, arouse expectation of fireworks. Nor is the reader disappointed, though the display is one of roman candles which emit bright lights of knowledge interrupted by good illustrations and occasional sparks rather than one of breath-taking jet-propelled rockets. Anatomy, physiology, and the routine clinical aspects of normal pregnancy and labour are excluded as "dreary irrelevance": and so they are—to those who already know them, as should the post-graduate students for whom this book must be intended. Professor Donald shows admirable courage in other ways too, and so far as possible shuns qualifying phrases. So aetiology and pathology are clearly stated and there are delightfully dogmatic accounts of treatment. Take, for example, puerperal deep thrombosis and embolism, conditions on which there still remains much vacillation on the part of clinicians: for these there is only one treatment—heparin intravenously in adequate doses accompanied by active movement of the patient; other anticoagulants, and even heparin intramuscularly, are condemned. By and large each chapter deals with a clinical problem—prolonged labour, antepartum haemorrhage, heart disease, symptom complexes, and the like. Recent authoritative articles on the various subjects have evidently been abstracted and combined to make a rational picture, due acknowledgments being given in short bibliographies. Contributors of chapters are H. M. Carey (toxaemia of pregnancy), G. W. Garland (malpresentations), Hilda Roberts (obstetric analgesia), and William Hayes (use and misuse of antibiotics). The contribution of the last-named calls for special commendation.

One striking and pleasing feature which reflects modern obstetric practice is the omission of any chapter on destructive operations on the foetus. Indeed, craniotomy is mentioned only twice—once in the treatment of hydrocephaly, and again (to be dismissed) in relation to outlet contraction.

The more one reads and re-reads various sections the more valuable this book appears to be for those who are regularly engaged in caring for pregnant and parturient women. There is no better concise yet reasonable statement of the modern practice of obstetrics. If there are too few frills for the embryo consultant, there are enough for the established one, and perhaps more than enough for the general-practitioner obstetrician. It is natural to wonder why Professor Donald has added to the very large number of works on obstetrics, and it is difficult not to conclude that he wrote this book for the fun of doing it. What better reason could there be, and what better guarantee of quality?

T. N. A. JEFFCOATE.

ARTERIAL THROMBOSIS

Congrès International de la Thrombose Artérielle. Organisé par la Station de Royat à l'Occasion du Centenaire de son Établissement Thermal, 6-7-8 Juin, 1953. Rapports et Discussions. (Pp. 320; illustrated. No price.) Paris: J. B. Baillière et Fils, Editeurs. 1954.

The *Reports and Discussions* of the International Congress on Arterial Thrombosis, which was held in June, 1953, at Royat, is now available. It covers a fairly wide field, and reflects very well the current opinion in France on this subject. As the title would indicate, the whole of the arterial system comes under consideration. Naturally a good number of the reports are concerned with the effects of thrombosis on the coronary arteries. To begin with there are three papers on the problems of the causes of unusual blood coagulation. The investigation of the lipoproteins by electrophoresis and the effects of infarction of the septum on the conducting tissues also receive consideration. Two papers deal with vectorcardiography, and there are two more on the surgical treatment of arterial thrombosis in the limbs. Some of the papers have references and some have summaries in English. The reports of the discussions are fairly short.

This book is a good summary of present-day views on arterial thrombosis in France and is well worth looking into. The paper is good and the illustrations are clear.

TERENCE EAST.

TECHNIQUES IN CLINICAL CHEMISTRY

Techniques in Clinical Chemistry: A Handbook for Medical Laboratory Technicians. By Frederick N. Bullock, F.I.M.L.T., F.R.M.S., F.C.S. (Pp. 171+ix; illustrated. 16s. 6d.) Bristol: John Wright and Sons, Ltd. 1954.

In *Techniques in Clinical Chemistry* the author has produced a useful book, more especially for the student and junior technician. This value is well shown in the first chapter, devoted to fundamentals, as even more advanced technicians often spend years carrying out complex biochemical investigations without any real knowledge of the

basic principles involved in the test, and more advanced and complete textbooks cannot spare the space for these very necessary explanations.

The chapter on specimen collection is clear in its instructions, but the suggestion that the measurement of 24-hour specimens of urine be carried out in the wards is a very retrograde step and would inevitably result in error. The instructions on the collection of faeces have one important omission—namely, the precise procedure in their collection over a measured period by using markers such as carmine or charcoal at the beginning and end of the test period. Most nursing staffs have, very naturally, great difficulty in grasping the principles of this procedure unless it is given in detail. In the chapters on blood analysis the methods are well described and alternative procedures given.

In the determination of blood chlorides, most workers have experienced difficulty in obtaining a sharp end-point with thiocyanate titration owing to the interaction of the silver chloride and iron thiocyanate. This can easily be avoided by making the silver-nitrate–blood-filtrate mixture up to a known volume, filtering, and titrating an aliquot of this filtrate, now free from silver chloride. The end-point is then sharp and persistent. The method of determining serum chlorides by direct titration with mercuric nitrate (Schales and Schales) should be included in another edition, as this is a great time-saver in a busy routine laboratory. Direct titration of the chlorides of cerebrospinal fluid with a chromate indicator has many advantages. In the section on phosphatases there might be more emphasis on the high levels of alkaline phosphatase in all forms of obstructive jaundice.

The urine section is well done, but some tests of rather doubtful value are included. Bence Jones protein is best identified by its low coagulation temperature and re-solution on boiling, or alternatively the procedure of Osgood and Haskins may be used. The salicyl-sulphonic acid and Bradshaw tests described are of no real value.

The author is to be congratulated on producing a very useful contribution to the routine chemical pathological laboratory equipment.

H. E. ARCHER.

FORENSIC PATHOLOGY AND TOXICITY

Legal Medicine: Pathology and Toxicology. By Thomas A. Gonzales, M.D., Morgan Vance, M.D., Milton Helpern, M.D., and Charles J. Umberger, Ph.D. Introduction by Harrison S. Martland. Second edition. (Pp. 1349+xii; illustrated. $22.) New York: Appleton-Century-Crofts, Inc. 1954.

The second edition of this authoritative volume by the Medical Examiners of the City of New York adds the experience of another 14 years of active practice and greatly increases the scope of the book. Its great virtue lies in the fact that it is based almost entirely on the personal experience of the authors, whose views are amply supported by an extensive bibliography which is completely up-to-date.

The Medical Examiners in New York are responsible for the investigation of deaths which in this country might be styled "coroners' cases." The investigation of some 20 000 deaths annually in the city is centralized and conducted by medical officers actively practising pathology, serology, and toxicology. While necropsies are conducted at several mortuaries, the actual statistical material is correlated in the Chief Medical Examiner's office, and the data so obtained between 1918 and 1951 have been incorporated in various chapters to indicate the frequency of deaths from natural and violent causes.

Since the edition of 1940 new chapters have been added on the necropsy findings on embalmed bodies—a difficulty not entirely confined to the United States—cardiac contusion, traumatic cerebral oedema, injuries in sport, the Rh factor, pathological findings in poison cases, uranium compounds, the recent organic drugs, and anaesthetic and operative deaths, while in the last six chapters a fresh approach has been made to the identification of poisons. This exhaustive analysis must be of great interest, not only to the forensic toxicologist but also to the hospital biochemist. Similarly the chapters on sudden and unexpected death contain much material of great value to the hospital pathologist.

The book is profusely illustrated with first-hand and first-class material, though some of the black-and-white reproductions of photographs are indistinct and require a more descriptive caption. It is expensive and essentially a book of reference, but as an exposition of modern knowledge of legal medicine it is without equal.

DONALD TEARE.

MOSQUITO BIONOMICS

Mosquitoes: Their Bionomics and Relation to Disease. By William R. Horsfall. (Pp. 723+viii. $16.) New York: The Ronald Press Company. 1955.

In preparing this work the author, himself a well-known authority on mosquito bionomics, has undertaken the formidable task of summarizing in a single volume all available information relating to this important subject. Preliminary consideration is given to the characteristics common to the sub-family as a whole and to those peculiar to each genus. Each individual species is thereafter treated separately in respect of nomenclature, subspecific variants, and synonyms, number of generations, and any known data regarding hybridization. The bionomics of the egg, larva, pupa, and adult insect are dealt with under separate headings, and the importance of each species in relation to the transmission of disease is fully discussed.

The bibliography contains references to more than 4,000 scientific works. To consult all these in the original would be beyond the capacity of any single individual, and the author has had perforce to rely in some cases on citations made by others. In such circumstances errors are unavoidable, as, for instance, where Natvig is quoted as stating that the work of Shute indicated that *Aëdes cantans* produces several generations every year; whereas in point of fact the latter author emphasized that this species, in common with *Aëdes punctor* and *rusticus*, has only a single brood each year. Such errors will no doubt be corrected in subsequent editions.

The general format of the volume is excellent; the mass of material is well arranged and clearly presented, data relating to lesser-known species being set out in tabular form. With the introduction of modern methods of mosquito control a detailed knowledge of the life history of each insect vector has become more essential than ever. The book will prove an invaluable work of reference, especially to those actively engaged in the control of mosquito-borne diseases.

GORDON COVELL.

Some years ago King George's Jubilee Trust instituted an inquiry into "the causes of wastage from youth organizations and to throw light on the problems of attracting to them boys and girls in the changed conditions of to-day, and of recruiting to their service men and women with the generosity and capacity to lead and inspire youth." The result has recently been published as *Some Young People*, compiled by Pearl Jephcott. The survey was conducted in several different areas: two in London, one in Nottingham, and two in Oxfordshire villages. The book gives a brief glimpse of some of the adolescents between 14 and 17 years of age who were interviewed; their backgrounds, interests, and forms of entertainment. It provides statistics of education and numbers in youth organizations. The report brings out the general apathy of adolescents towards a creative use of their leisure time. Various reasons are given for the lack of response to the aims of youth organizations: shyness; dislike of further control and discipline; the number of young members; the fact that the leaders are often middle-aged and possibly out of touch with the ideas of youth—to name only a few. In conclusion the report stresses the importance to the adolescent of personal contacts and the example of adults in their daily lives. *Some Young People*, which is published by George Allen and Unwin Ltd., 40, Museum Street, W.C.1, costs 12s. 6d.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY MAY 7 1955

NEW WORK ON TRANSPLANTATION

The likelihood of surgery making another great step forward—on the same scale as the advances resulting from the discoveries of anaesthesia and asepsis—may depend on finding a solution of the homograft problem, so making it possible for surgeons to transplant skin grafts, kidneys, and other tissues and organs from one individual to another. This would be a great accomplishment, not all the benefits of which can at present be foreseen. Research on the problem is not lacking. Three symposia[1] have been devoted to it in recent years and more are planned. Indeed, in the laboratory the problem has already been solved, but in a way that does not lend itself to clinical application. R. E. Billingham, L. Brent, and P. B. Medawar[2 3] have shown that skin homografts (the most intractable of all) can be successfully exchanged between adult mammals or birds by taking advantage of the phenomenon which they call actively acquired tolerance. The principle underlying it is simple. It is a commonplace of immunology that embryos and very young animals cannot form antibodies, and that their only defences against infection are those which have been acquired at second hand. The novelty of the concept of tolerance lies in the demonstration that an animal's power to react against a specific antigen may be permanently impaired and perhaps completely abolished by exposing it to that antigen before its immunological faculties have matured. Thus a skin graft can be successfully transplanted from one adult to another, A to B, if B was injected in foetal life with cells derived from A. The embryos so treated not only fail to react against the tissue antigens: they may never acquire the capacity to do so in later life. The inhibition is highly specific; animal B becomes tolerant of tissues grafted from A, but remains as intolerant as ever to tissues grafted from another donor, C. Acquired tolerance may not be a general phenomenon in immunology, though both theory[4] and practice,[5] so far as they go at present, suggest that it probably is. Its theoretical importance is obvious. Biochemistry would not be the science it is if there were no specific inhibitors, but only substrates, to work with. Immunology has hitherto had no specific inhibitors in its armoury: "tolerance" may fill the gap.

A second important contribution has been made by N. A. Mitchison,[6] who found that transplantation immunity could be passively transferred from an immunized to a normal animal. He removed the regional lymph nodes—those which drained the grafted areas—from an actively immunized mouse and transplanted them into a second mouse belonging to the same strain. This second host thereupon behaved exactly as if it had itself been actively immunized—and so, in a certain sense, it had been. The transfer could not be carried out in the orthodox way by serum, nor by nodes other than those draining the grafted area, nor by dead cells of any kind. Mitchison's work has been fully confirmed by Billingham, Brent, and Medawar,[7] and both parties are agreed that the transfer is not brought about by preformed antibodies or by antigens carried over from the donor of the lymph nodes to their recipient. The term "passive immunity" is therefore inappropriate or misleading, and "adoptive immunity" has accordingly been proposed.[7] Mitchison's work shows that transplantation immunity is orthodox enough in one sense—namely, that the seat of the host's reaction against homografts is the regional node.

In one other respect it is clearly unorthodox, at least when judged by the standards of bacterial immunology. Free serum antibodies are exceedingly difficult to detect, and the homograft reaction cannot be reproduced *in vitro*. It seems to be necessary that the antibodies should attack the homograft *in vivo*, in a vascular situation, and it is at the vascular frontiers of the graft that the first signs of distress are revealed.[8] By complex and indirect means, protective antibodies have nevertheless been demonstrated by P. A. Gorer[9] and by R. E. Billingham and E. M. Sparrow[10]; agglutinating antibodies are also formed, as Gorer has long since demonstrated, and may agglutinate leucocytes[11] as well as red blood cells. Unfortunately, there are grounds for reasonable doubt about the effectiveness of agglutinins in the homograft reaction, and until these doubts have been cleared up their status will remain obscure.

The reaction against homografts has every distinguishing mark of an immunological process. At one

[1] Tissue Transplantation Conference, Arden House, 1952: see *J. nat. Cancer Inst.*, 1953, **14**, 667–767. Ciba Foundation, 1953: *Preservation and Transplantation of Normal Tissues*, 1954, London. *Ann. N.Y. Acad. Sci.*, 1955, **59**, 277–466.
[2] Billingham, R. E., *et al.*, *Nature, Lond.*, 1953, **172**, 603.
[3] —— *et al.*, *Ann. N.Y. Acad. Sci.*, 1955, **59**, 409.
[4] Burnet, F. M., and Fenner, F., *The Production of Antibodies*, 1949, Melbourne.
[5] Buxton, A., *J. gen. Microbiol.*, 1954, **10**, 398. Kerr, W. R., and Robertson, M., *J. Hyg. (Lond.)*, 1954, **52**, 253. Hanan, R., and Oyama, J., *J. Immunol.*, 1954, **73**, 49.
[6] Mitchison, N. A., *Proc. roy. Soc. B.*, 1954, **142**, 72.
[7] Billingham, R. E., *et al.*, ibid., 1954, **143**, 58.
[8] Taylor, A. C., and Lehrfeld, J. W., *Plast. reconstr. Surg.*, 1953, **12**, 423.
[9] Gorer, P. A., *J. path. Bact.*, 1942, **54**, 51.
[10] Billingham, R. E., and Sparrow, E. M., *J. exp. Biol.*, 1954, **31**, 16.
[11] Amos, D. B., *Brit. J. exp. Path.*, 1953, **34**, 464.
[12] Schinkel, P. G., and Ferguson, K. A., *Aust. J. biol. Sci.*, 1953, **6**, 533.
[13] Good, R. A., and Varco, R. L., *J. Amer. med. Ass.*, 1955, **157**, 713.

time, when the modern study of homografts was only beginning, evidence of conformity to the orthodox pattern was eagerly sought, and duly found. Departures from orthodoxy can now be looked for with an easy conscience, and it is quite possible that an entirely new kind of immunological response may be found. There is some evidence, for example, that immunity against homografts can develop long before immunity against bacterial antigens and distantly foreign proteins. Sheep are already able to react against homografts when only two-thirds of the way through foetal life (though already more highly developed, in an anatomical sense, than a newborn mouse).[12] This is a remarkable fact, for foetal sheep, like other foetal ungulates, are—in a literal but not clinical sense—agammaglobulinaemic: they acquire their gamma globulins, with their antibodies, after birth, and only later on do they begin to make their own. R. A. Good and R. L. Varco's recent demonstration[13] that an agammaglobulinaemic boy had no power to react against skin homografts is good evidence that the reaction against homografts is immunological; but it is not (and does not purport to be) evidence that the reaction is mediated by orthodox antibodies present in the gamma globulin fraction of blood. The cautious inference is that the failure of immunological mechanisms which has agammaglobulinaemia as one of its symptoms has tolerance of homografts as another.

CYCLOSERINE

The daily press on both sides of the Atlantic reported last February the discovery of a new antibiotic for the treatment of tuberculosis. The basis of the report was a paper read to the 14th Veterans Administration Conference on the Chemotherapy of Tuberculosis held at Atlanta last February. This paper, by I. G. Epstein, K. G. S. Nair, and L. J. Boyd[1] has now appeared in print, following another by H. Welch, L. E. Putnam, and W. A. Randall[2] of the Food and Drug Administration, Washington, which gives a little more information about this antibiotic. It appears to have very unusual properties, and some surprise may be felt that it should have had fairly extensive clinical trial before any announcement had been made of the results of such laboratory studies as usually precede this. The information about these studies is still very scanty—it is merely stated, for instance, that the antibiotic has "an extremely low toxicity," a future paper in confirmation being promised—and on what seems a slender basis some speculative ideas are put forward about its mode of action.

[1] *Antibiot. Med.*, 1955, 1, 83.
[2] Ibid., 1955, 1, 72.

Cycloserine is produced by *Streptomyces orchidaceus* and was discovered by members of the staff of the Commercial Solvents Corporation. Eli Lilly and Co. have collaborated in its study and their trade name for it is "seromycin." It is water-soluble, has a molecular weight of only 102, and, as would be expected from so small a molecule, appears to be freely diffusible: the concentrations attained by the drug in the cerebrospinal fluid, pleural fluid, and sputum are said to be approximately equal to those in the blood, though the published papers give no detailed particulars. Minimum inhibitory concentrations for various bacteria as determined by Welch and his colleagues were mostly from 50 to 250 μg./ml., Gram-positive and Gram-negative species being about equally susceptible. There is no description of how these tests were done; hence it remains possible that by varying some factor, such as inoculum size or the composition of the medium, a degree of *in vitro* activity might be demonstrated which would accord more closely with that thought to have been observed *in vivo*. The list of species tested does not include *Myco. tuberculosis*, and indeed there is no information at all in either paper about the *in vitro* activity of cycloserine against this organism except in a footnote giving the findings of two other workers, between which there is a twelve-fold discrepancy. Presumably much more extensive and positive information on this vital matter will be forthcoming shortly. The paper by Welch and his colleagues also reproduces some of the data in personal communications from two surgeons who have used cycloserine for the treatment of urinary tract infections with some success: not enough information is given to judge the degree of this. It finally records the results of a pharmacological study in 40 normal subjects given single and repeated doses in oral capsules. The blood and urine concentrations attained were high and remarkably sustained, and repeated doses had a cumulative effect, reaching a maximum in three days of about 50 and 1,000 μg./ml. in the blood and urine respectively. It seems, therefore, that part of what cycloserine lacks in antibacterial activity it compensates for by the high concentrations attained in the body. Nevertheless these authors think these concentrations inadequate to explain the therapeutic effect, and speculate on other possible modes of action—"... the production of physiologic conditions in the host, resulting in a more unfavourable environment for multiplication or survival of micro-organisms," or "the production of humoral factors that act with the drug in combating infections."

The paper by Epstein and his colleagues, which deals exclusively with the treatment of pulmonary tuberculosis, is strongly reminiscent of the enthusiastic

first reports on the effects of isoniazid in 1952. Even patients with far advanced disease unresponsive to previous chemotherapy began to gain weight and had less cough and sputum : of 29 such patients, 22 became sputum-negative and 20 showed radiological improvement. Eight further patients with more recent and previously untreated, though extensive, disease, classified as moderately advanced in four and far advanced in four, were treated with evidently more dramatic results : fever abated promptly and weight gains were up to 23 lb. (11.5 kg.). All showed radiological improvement and all became sputum-negative. There is no information about any tests of the sensitivity of these patients' tubercle bacilli to cycloserine, though it is said that " an extensive study is now under way " to obtain data on the emergence of resistant organisms. Yet the authors subscribe to the idea in the previous paper that " cycloserine owes its salutary effects *in vivo* to factors not directly connected with its *in vitro* antibiotic activity." There seems to be no need for this assumption if one of the two discrepant figures obtained by other workers is accepted as the minimum inhibitory concentration of cycloserine for *Myco. tuberculosis*. This, obtained with the H37Rv strain, was 2.5–5.0 μg./ml., well below the concentration maintainable in the blood. It has also to be remembered that so diffusible a substance may penetrate infected cells and perhaps avascular lesions much more readily than other drugs. It is profitless to speculate further on fragmentary data, and the process of filling the gaps in this story will be watched attentively.

HEALTH SERVICES IN INDIA

A Health Survey and Development Committee was set up by the Government of India about fifteen years ago and reported in 1946, with blueprints for future health activities. At that time the maternal mortality rate was 20 for every 1,000 live births ; the expectation of life for the Indian was 27 years ; the proportion of qualified doctors to the population was one in 6,300 ; and the average population served by a hospital or dispensary in rural areas was 50,000, and in urban areas 30,000. The *India 1954 Annual Review*[1] does not contain up-to-date figures, but even by 1951 all the mortality rates seem to have fallen (the infant mortality rate from 158 to 124.4), and the expectation of life had risen to 32 years. The number of medical colleges had increased by 50%, and the annual admissions of students had almost doubled. There was a recession in deaths from infectious diseases, plague was on the wane, and malaria was less of a scourge. The health section of the *Annual Review* is written by Rajkumari Amrit Kaur, the Minister of Health. She mentions that one of her first acts as Minister was to end the dichotomy between curative and preventive health services by combining the functions, discharged hitherto by separate bodies, of medical and public health advisers, and to commend similar action to the States, nearly all of which followed the central example. The result has been greater co-ordination and team-work. The comparative isolation of the independent medical profession from the official health " hierarchy " is also being ended.

A state health insurance scheme for industrial labour has been started during the last three years. At present it embraces only 60,000 workers, but with its extension to Bombay it will cover half a million. Another health insurance scheme has been started by the central Government for its staff in the capital city and covers a quarter of a million persons for general practitioner, specialist, and hospital services. These efforts touch only the fringe of the problem, but the Minister says they are indications of the trend. A national malaria control programme was launched two years ago and is making rapid strides against a disease which in 1946 was estimated to affect 100 million people and to cause two million deaths. Nearly 90 antimalarial units, each covering a population of one million, are already in operation, and another 35 are coming into existence shortly. By the end of the second five-year plan (1961) it is hoped that malaria will be under control. Tuberculosis, too—with an average number of deaths in a year amounting to 500,000—is being actively combated. A mass B.C.G. vaccination scheme has 120 teams in the field, and they have tested 33 million persons and vaccinated one in three. An All-India Institute of Medical Sciences—costing about £3,750,000—is expected to be inaugurated within the next two or three years. It will combine undergraduate and postgraduate education with research, and will turn out, it is hoped, an increasingly large number of well-trained teachers for the medical colleges. Acts relating to the professions of pharmacy, nursing, and dentistry have recently been passed, and legislation is being considered for the prevention of practice by unqualified and unregistered persons, and for the regulation of the training which is given in indigenous systems of medicine.

Family planning movements are gradually taking shape, assisted by many independent and voluntary organizations. This has a direct bearing on the food problem of India, and here again progress is being

[1] Published by the Information Service, India House, Aldwych, London, W.C.2.

made. The five-year plan fixed an increase of 7.6 million tons in cereal output by 1955–6, and already the estimated increase in 1953–4 is 9.5 million tons. Before the relaxation of controls in the middle of 1952, 108 million people were subject to rationing. A year ago the number had dropped to 44 million, and to-day rationing is only a memory. These are all encouraging signs that the Government of India is grappling successfully with health and social problems which, in spite of recent efforts, remain of enormous complexity, for the inhabitants of India number about one-seventh of mankind.

PUBLIC HEALTH SALARIES

It is four and a half years since the salaries of medical men and women in the public health service were raised in accordance with the terms of the award[1] of the Industrial Court, to which, in 1950, the staff and management sides of Whitley Council Committee C agreed to submit their differences. Although the staff side did not get all it wanted from that award, there was satisfaction that substantial gains had been made. Nevertheless the award to assistant medical officers was disappointingly small—the salary being on a scale from £850 to £1,150 per annum. The staff side made persistent efforts to have this improved without success, and again, in 1953, the differences between staff and management on this point had to be resolved by the Industrial Court. The salary awarded[2] this time to assistant medical officers was £950 rising to £1,300. Meanwhile all the other medical officers in the public health service have been paid salaries at the rates awarded in 1950.

The case for improving these salaries has been overwhelming for some time past, for not only has there been a great rise in the cost of living, but members of the public health service have seen their colleagues in general practice benefit from the Danckwerts award in 1952 and their colleagues in the hospital service from the increases negotiated last year. But once again the two sides of Whitley Committee C failed to agree on the amounts by which public health salaries should be increased and once again the differences were laid before the Industrial Court. The dispute was clear cut. The staff side urged the Court to take into account the salaries being paid to doctors in other branches of the Health Service; whereas the management side "felt that it would be right to give increases of such an amount as would bring the salaries of medical officers of health into line with those of the other professional officers (in local government) of comparable status" (who, it may be said, had negotiated certain percentage increases to take effect from January 1 this year). The award announced last week and published in the *Supplement* this week (p. 214) shows that the Court has favoured the management side's view, though this result cannot have been due to any fault in presentation of the staff side's case: scrutiny of the minutes of the proceedings of the Court shows how cogently this was argued by counsel briefed by the Public Health Service Defence Trust.

The immediate effect of the award will be some disappointment that the staff side's reasonable requests have not been met, but also some satisfaction that the increases which have been granted will help to ease the financial burdens that fall particularly heavily on salaried medical men and women whose earnings are definitely on the low side for highly trained professional people. These increases, as can be seen from the details in the *Supplement*, amount to about £175 a year for medical officers of health in areas with a population not exceeding 100,000 and about £200 a year in areas where the population is over that figure; senior medical officers obtain a rise of £165 per annum at the minimum of the scale and £180 at the maximum; and assistant medical officers (who, as stated above, had the minimum of their salaries raised by £100 and the maximum by £150 under the 1953 award) go up another £25 at the minimum end of the scale and £75 at the maximum (£1,375 under the new award). Under a previous agreement[3] the salaries of deputies are linked with those of their chiefs (66⅔% of the minimum scale adopted by the employing authority for the post of medical officer of health, with annual increments equivalent to those of the M.O.H.); and the staff and management sides had already announced that, when an award was made in respect of the three groups of officers specifically dealt with, they would be able to reach agreement on the salaries of the remaining categories of medical officers of health. In so far as they go, then, these awards will bring public health salaries nearer to the incomes of doctors in other branches of medicine. But the long-term effect on the National Health Service of the management side's obstinate resolve to keep the salaries of medical officers of health linked with those of other chief officers in the local government service is difficult to foresee, for, as one observer[4] has put it, "One of the chief failures in co-operation between the hospital and local health authority service lies in the division of the medical profession into two salaried camps of grossly unequal status."

CANCER AND THYROID ACTIVITY

The discovery that the incidence of a disease corresponds with that of some social, physiological, or other peculiarity in the population or milieu is sometimes a first step towards learning how to overcome the disease or unravel its aetiology. Sceptics may say that many statistical correlations of this kind have been found in the past which seem to have led nowhere—but that may be because the story is not yet finished. Cancer research has shown several times that many years may elapse between the discovery of a correlation and the beginning of any serious attempt to explain it. In 1844

[1] *British Medical Journal Supplement*, 1950, **2**, 255.
[2] Ibid., 1953, **1**, 278.
[3] Ibid., 1951, **1**, 209.
[4] Dr. W. G. Patterson, speaking at the Royal Sanitary Institute in London on March 9, 1955.

R. Stern[1] found from a study of Verona's statistics that breast cancer was more frequent in single than in married women, but 70 years passed before his observation was confirmed and its important implications began to be considered. In 1868 A. Haviland[2] addressed the Medical Society of London on the relationship between cancer death rates and geology in the registration districts of England and Wales, but only recently has serious research begun on soil in connexion with certain forms of cancer.

Another example concerns a statistical association between cancer and hypothyroidism, for which evidence was produced by Percy Stocks[3] in 1924, following a suggestion by Bayard, of Zermatt, in 1919. By dividing Switzerland into 31 areas and correlating standardized death rates for cancer of the digestive tract in 1920 with the goitre frequencies in army recruits in 1921–2, Stocks obtained a coefficient of +0.636. He also found that the proportion of malignant growths comprised by cases of stomach cancer was positively related to the frequency of goitre in the U.S.A. and parts of Norway as well as in Switzerland. This was supported by the finding that thyroid anomalies were recorded in 21% of necropsies on cancer patients at the Middlesex Hospital, whereas the same pathologist had recorded them in only 4% of patients who had died from diseases other than cancer. A comment in this *Journal*[4] on that paper remarked that "the refined analysis of cancer rates is an arduous task; he who undertakes it must be prepared for many disappointments." Thirty years have been a long time to wait for any direct follow-up of these findings, but now J. G. C. Spencer[5] has re-examined the problem and produces confirmatory data of an association between cancer and goitre frequencies in other countries. He gathers together recent clinical, experimental, and pathological observations suggesting that the thyroid has some influence on the development of cancer.

O. Bayard[6] thought that deficiency in the supply of thyro-iodine to cells might cause premature ageing of the tissues, and Spencer mentions the lower metabolic rate in diabetics as perhaps accounting for their raised liability to cancer, as found by Joslin. He suggests that the increased demand for iodine at puberty and during pregnancy may account for the greater likelihood of melanomata developing at those times. Animal experiments, cited by Spencer, have shown that administration of thyroxine in the diet is prejudicial to successful grafting of certain tumours from one mouse to another, and that simultaneous thyroxine injection reduces the tumour response to injection of dibenzanthracene, whereas feeding with thiouracil enhances the response. Regression of rat tumours has been brought about by natural thyroxine; and the increased rate of development of spontaneous mammary tumours in mice during pregnancy might, he thinks, be due to thyroid deficiency.

The therapeutic administration of oestrogens is believed to influence cancer growth indirectly by suppressing pituitary activity. Spencer argues that a high thyroxine level in the blood produces a similar effect and that thyroxine has advantages over oestrogens in that it is not carcinogenic, the pituitary is not known to become indifferent to it in time, and thyroxine in the tissues makes an environment unfavourable to tumour growth. The author is careful to point out: "A low metabolic rate or an insufficiency of thyroid substance can in no way be considered as a primary cause of cancer. Thyroid and related substances cannot therefore be considered as a cure for cancer. It is, however, suggested that thyroid function (or dysfunction) may be associated with the susceptibility or immunity to cancer." A. A. Loeser[7] has advocated the administration of thyroid as an ancillary to the surgical and other treatment of cancer; and he and Spencer also suggest that, as a preventive measure, maintenance of a good level of thyroid activity during middle life might increase immunity to the action of carcinogenic substances. It is good news that long-term research on this important matter has been started at the Frenchay Hospital, Bristol, and that further papers may be expected when data become available.

[1] Stern, R., *Ann. univ. di Medicina*, 1844, **110**, 444.
[2] Haviland, A., Lecture to Medical Society of London, Nov. 30, 1868. Privately published, London, 1869.
[3] Stocks, P., *Biometrika*, 1924, **16**, 364.
[4] *British Medical Journal*, 1925, **1**, 85.
[5] Spencer, J. G. C., *Brit. J. Cancer*, 1954, **8**, 393.
[6] Bayard, O., *Beiträge zur Schilddrüsenfrage*, 1919, Basel.
[7] Loeser, A. A., *British Medical Journal*, 1954, **2**, 1380.

NOMENCLATURE AND MORBIDITY SURVEYS

Team-work in medical research has a long history, as was made clear at a recent meeting of the Section of General Practice at the Royal Society of Medicine, when Dr. R. M. S. McConaghey[1] gave a historical review of collective medical investigations in this country based on observations and records of individual practitioners during the eighteenth and nineteenth centuries. Moving forward to a much more recent period, there has been the exploratory study by the General Register Office[2] in which about ten practitioners took part for several years: this has formed the basis for a much expanded twelve-month survey of morbidity in general practice which has started this month, organized jointly by the College of General Practitioners and the General Register Office, and in which over 100 general practitioners are taking part. As the latest Research Newsletter[3] of the College observes, those taking part in the inquiry are going to face various difficulties, and one of these will be the nomenclature of the minor complaints seen so frequently in general practice, for which each doctor has his own favourite label and which may mean something quite different to his colleagues.

Medical statisticians make a clear distinction between "nomenclature" and "statistical classification" of

[1] Meeting of Section of General Practice on April 20, 1955.
[2] Logan, W. P. D., *General Practitioners' Records*, General Register Office Studies on Medical and Population Subjects, No. 7, 1953, H.M.S.O., London.
[3] *Practitioner*, 1955, **174**, 601 (College of General Practitioners Research Newsletter No. 6).
[4] *The Nomenclature of Disease*, 1948, H.M.S.O., London.
[5] *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*, 1948, W.H.O., Geneva.
[6] *Standard Nomenclature of Diseases and Operations*, 1952, New York.

diseases. Basically, a medical nomenclature is a catalogue of approved terms, which has to be extensive so that every morbid condition that can be specifically described has its specific designation recorded. On the other hand, a statistical classification is intended for a quite different purpose—namely, to group diseases together that have something in common, so that their statistical study will be facilitated. The complete specificity of a nomenclature limits its suitability for use as a statistical classification, whereas a classification is not designed to guide doctors in their choice of the most acceptable medical terms. There is therefore a very clear difference, both in purpose and in content, between the *Nomenclature of Disease*[4] of the Royal College of Physicians and the World Health Organization's *International Statistical Classification of Diseases, Injuries, and Causes of Death*,[5] the seventh revision of which is now in course of preparation after the customary international revision conference in Paris in February of this year. Another important and well-known work is the American *Standard Nomenclature of Diseases and Operations*,[6] which is primarily a nomenclature, as its title indicates, but contains cross references to corresponding categories in the *International Classification* and has been so constructed as to serve certain classificational purposes such as the indexing of hospital clinical records. Opinions differ about its advantages for this purpose over the *International Classification*, which, with appropriate *ad hoc* expansions, is being used successfully as a diagnostic index in a number of hospitals in this country.

The special problems of nomenclature and classification of minor symptomatic conditions will no doubt be engaging the minds of those responsible for the new morbidity survey in general practice, and it will be seen in due course whether the chosen methods of classifying disease will be adequate to cope with the vagaries of diagnostic terminology that the survey will encounter. It may be, as the College's Newsletter suggests, that a completely new approach to the nosology of the minor maladies met with in general practice is long overdue.

PARALYSIS FOLLOWING POLIOMYELITIS VACCINATION

Current reports that a number of children in the United States inoculated with the new poliomyelitis vaccine have since developed paralysis have come as an unwelcome shock after the exciting news of a fortnight ago. The present situation is obscure owing to a virtual absence of any concrete facts, but it would appear from reports in the American and British press that between 29 and 35 inoculated children have developed paralytic poliomyelitis. Two deaths are reported.

After the news of last year's vaccine trials, a large quantity of vaccine was released for use in the United States. The U.S. Public Health Service states that so far 2,270,000 children have been vaccinated in 42 states. Of these, 300,000 have received a vaccine prepared by the Cutter Laboratories, Berkeley, California, and it would appear from press reports that 26 of the 29 paralytic cases were vaccinated with material from this source. A further report states that at least 10 of these 26 cases received vaccine from the same batch.

This is disquieting news. With the facts available three main possibilities for such an incident must be considered. First, it could be chance, the vaccine having been given just prior to the onset of poliomyelitis which would have developed in any case. Again, if the facts are correct, 26 cases from one source is rather too large a number for coincidence, and the figures for the weekly incidence of poliomyelitis (106) in 42 states do not suggest any major prevalence at present. The second possibility is the association between paralytic poliomyelitis and parenteral injections first described in this country by Martin,[1] and in Australia by McClosky.[2] In these cases paralysis followed immunization with diphtheria, pertussis, and combined prophylactics. These findings have been confirmed,[3] but the onset of paralysis nearly always seems to occur between 8 and 28 days after inoculation. Bodian[4] has provided experimental evidence to support the idea of the "provoking action" of trauma. In these recent reports from the U.S.A. the time interval appeared to be less than a week in some cases. What is not known is how many injections had been received. The third possibility is that live virus was present in a proportion of the formolized vaccine. This is the crucial consideration. Twenty years ago Leake[5] reported a series of 12 cases of poliomyelitis in children receiving a chemically treated anti-poliomyelitis vaccine. Six children died. All 12 children had had an injection between 8 and 27 days before symptoms, and of these 8 had had a second injection between 1 and 6 days before symptoms. It is possible that if live virus were present the time interval between injection and the onset of paralysis might be shorter than in those cases already referred to following parenteral injection.

From the report in last week's *Journal* of the preliminary finding of the 1954 trials it appeared that the vaccine used in the trials was safe, and there is no cause to alter that opinion. It is by no means clear whether the same safety tests apply to-day. Unquestionably the most important requirement of a vaccine is its safety, and the tests to ensure this must be strict indeed. Meanwhile the general vaccination programme in the U.S.A. is continuing. Let us hope that before long the answer to the problems posed by the recent events in the United States will be forthcoming.

The next session of the General Medical Council will open on Tuesday, May 24, at 2 p.m., when the President, Sir David Campbell, will take the chair and deliver an address.

[1] Martin, J. K., *Arch. Dis. Childh.*, 1950, **25**, 1.
[2] McClosky, B. P., *Lancet*, 1950, **1**, 659.
[3] Hill, A. B., and Knowelden, J., *British Medical Journal*, 1950, **2**, 1.
[4] Bodian, D., *Amer. J. Hyg.*, **60**, 1954, 358.
[5] Leake, J. P., *J. Amer. med. Ass.*, 1935, **105**, 2152.

EMERGENCIES IN GENERAL PRACTICE

ANTE-PARTUM HAEMORRHAGE

BY

FRANK STABLER, M.D., F.R.C.S., F.R.C.O.G.

Assistant Gynaecologist, Royal Victoria Infirmary, Newcastle-upon-Tyne

It is proposed to discuss ante-partum haemorrhage not from the aspect of its types and their subdivisions, nor from that of its operative treatment, but from the aspect of the family doctor called to a patient's house in the later months of pregnancy because there is bleeding from the vagina.

The term "ante-partum haemorrhage" is restricted to bleeding after the twenty-eighth week of pregnancy. Its pathology is no different from bleeding earlier in pregnancy, but its consequences are likely to be more serious to the mother and management may need to take into consideration the life of the foetus. That it may be a serious condition is shown by the fact that it is still the fourth commonest cause of maternal death in England and Wales. The early management of these cases is of critical importance, and I hope to make it evident that what is *not* done is as important as what is done. The practitioner's first concern when called to his patient will not be whether she has placenta praevia, accidental haemorrhage, cervical polypus, carcinoma of the cervix, or a ruptured vaginal varix, but how much blood has been lost and what is her general condition.

Slight Haemorrhage

Slight haemorrhage has occurred and there is no disturbance of the woman's general condition.—To attempt to make an exact diagnosis is dangerous and unnecessary. Overshadowing all the management is the fact that the bleeding may be the first warning haemorrhage of placenta praevia. It is possible that vaginal examination will bring on profuse and dangerous bleeding. Even rough abdominal examination might lead to further bleeding. Gentle abdominal examination may show that the presenting part is in the pelvis. In this case, though placenta praevia is not excluded, one can say that a dangerous degree of praevia is not present and that the urgency is not great. If the presenting part is not engaged the diagnosis is not helped. If a high head or any malpresentation is found it is likely that a dangerous degree of placenta praevia is present. An unusual feature is that the primigravida is likely to be safer than the multigravida. Very seldom does the primigravida go on to profuse and alarming haemorrhage after the first show. The multigravida with her slacker, more accommodating uterus may have a drenching loss as the first evidence of the condition. If the foetal heart rate is altered the case is more likely to be one of accidental haemorrhage.

Without further ado every one of these patients should be referred to hospital for admission. There are many maternity units and nursing-homes staffed by general practitioners, and with his patient admitted the doctor may permit himself a further examination. He might examine with a Sims speculum to exclude polypus, carcinoma, and ruptured vaginal varix. Expert assistance is needed for the treatment of each of these. The removal of polypi from the cervix in pregnancy may lead to severe bleeding needing cautery or suture. The mattress suture needed for ruptured varices may bleed severely from the needle punctures. Carcinoma is of course a rare and dangerous problem.

A woman at the thirty-seventh week of her second pregnancy had a slight, painless loss. Without attempting to make a diagnosis her doctor sent her into hospital. She arrived in perfect condition. After a week in bed in hospital there had been no further bleeding. The baby was lying somewhat obliquely with the head in the left iliac region. It was decided to examine her vaginally in the operating theatre, with everything set ready for caesarean section. A postgraduate class was invited to attend this examination. The apparently normal cervix was inspected and through the fornices a boggy mass could be felt. In order to press home the lesson that these cases should not be examined vaginally except under these special circumstances I passed a finger through the os, expecting a trickle of blood to ensue. When the finger was withdrawn a cascade of blood followed and soon began to form a steadily enlarging pool on the table. A rapid caesarean section ensured that neither mother nor baby came to any harm, but the class, and I, received a smart lesson.

Moderate Haemorrhage

Haemorrhage sufficient to affect the woman's general condition has occurred.—Here the practitioner's dilemma is not which cases should be sent to hospital (all should) but whether preliminary treatment is necessary before doing so. Let it be said at once that no woman who is still bleeding should be sent on an ambulance journey without some method of stopping the haemorrhage or of making up for what is lost. If pain is present, and especially if there are some evidences of toxaemia, the bleeding is likely to be due to accidental haemorrhage, but this does not affect the management. In all cases an intramuscular injection of ¼ gr. (16 mg.) of morphine should be given. The attendant should then consider such factors as the distance from the hospital, whether labour pains have started, the parity of the patient, how much blood has been lost, whether bleeding is still going on, and the aspect of the patient. I write "aspect," for one glance at a woman's face tells more than exact measurements of blood pressure and pulse rate. Indeed the blood pressure may be gravely misleading because of previously present hypertension.

He will lean towards immediate dispatch to hospital in those patients whose loss has not been excessive, those who have pain, and in primigravidae, but will not send in one who is still bleeding. For the rest there should be no woman in Great Britain beyond the reach of a domiciliary emergency service (the flying squad), or at least of a resuscitation organization. Whilst awaiting the arrival of the squad the patient should be induced to lie still and quiet. A tight binder may be applied. No doctor should ever feel at all guilty of having made a fuss if the squad arrives and finds the patient in quite good condition : he should feel proud. The converse is dreadful. An alarmed doctor makes hurried arrangements to bundle his patient into an ambulance and so out of his responsibility. One still hears of these patients arriving at hospital dead or expiring. In the experience of the Newcastle Obstetric Emergency Service all cases of accidental haemorrhage will need to be transported to hospital, but many of them will need transfusion of blood before the journey is made. Certainly all patients with placenta praevia will need admission. These emergency cases should all be given Group O rhesus-negative blood, for even if their grouping has been tested there are possibilities of error, technical and clerical. Once Group O rhesus-negative blood has been transfused it is best to continue with this even if the correct blood group has been ascertained.

A doctor's wife had been quite well in her fourth pregnancy until at the thirty-second week she awoke at 4 a.m. to find herself wet. Her husband found her to be in a pool of blood. He called his partner, who gave her morphine, sent for the flying

squad, and did no more. On the arrival of the squad her blood pressure was 60/40, pulse rate 82, and she had fainted twice. By 5.10 a.m. the second pint of blood was running in rapidly. A tight binder was applied and by 6 a.m. she was in hospital with a blood pressure of 100/70 and a pulse rate of 100. There was a stage IV placenta praevia. At 9 a.m. a caesarean section was done. In all 5 pints (2.8 litres) of blood was transfused. She left hospital with a haemoglobin of 82% and a baby thriving on the breast.

Alarming Haemorrhage or Severe Shock

The haemorrhage is alarmingly severe or the patient shows severe shock or pain.—There may again be placenta praevia, or there may be concealed accidental haemorrhage or, rarely, a true couvelaire uterus ("apoplexie uteroplacentaire"). According to the degree of unexpelled blood so will be the degree of shock, until in the worst cases one finds a woman with ashen lips, dilated pupils, collapsed or anxiously restless, with hard tender uterus and in severe pain. All of these patients should be given an intramuscular injection of ¼ gr. (16 mg.) of morphine as a first step. None of them should be packed into an ambulance forthwith. Raising the foot of the bed is an ineffective procedure. To have any effect on the circulation the feet need to be 18 in. (45 cm.) above the head, and if this is done any benefit is counteracted by the repeated disturbance necessary to prevent the patient sliding into the bed-head. Overheating should be avoided. The cold skin is an evidence that the body is withdrawing blood to more vital parts. Heat will cause skin vasodilatation and lower the blood pressure further. Blood transfusion is imperative and should precede the ambulance journey or be given during it. If she is left quiet very seldom will a woman fail to improve. The initial catastrophe is usually followed by a rebound. It takes time for the body to muster its resources of hypotension and vasoconstriction, and once these are in action a temporary improvement sets in. By then the squad should have arrived. Manipulations and intervention can only add to the seriousness of the condition unless and until an improvement has been achieved by natural or surgical means.

What should be done if the patient is remote from help and transfusion is not available for at least an hour? To stand idle for longer than this may seem to imperil the patient's life. Many doctors keep a flask of dextran solution and a giving set ready for these emergencies. They should certainly be employed. The solution keeps indefinitely and will maintain blood volume effectively until such time as blood is available. The membranes may be ruptured artificially under certain circumstances: when one is sure that a placenta praevia of severe degree is not present (for example, when the presenting part is well engaged in the pelvis), when recurring labour pains are present, when the woman is a multipara, and especially if labour is premature. The first condition is the most difficult to fulfil, but it is the most important, for to attempt to rupture membranes when the placenta covers the os is dangerous.

Vaginal Plugging and Bimanual Compression

What is the attendant to do with a patient steadily bleeding and deteriorating and help is to be long in coming? Is there no means of staunching the flow as a first-aid, temporary measure? The old-fashioned vaginal plug is an effective means of stopping any ante-partum bleeding, but it was abandoned because it was almost never applied efficiently in domiciliary practice. To apply it certainly needs a general anaesthetic. Up to half a pound (0.22 kg.) of cotton-wool will be needed, and this, soaked in saline, will half fill a bucket. Each pledget when wrung out is packed into the vagina until it is distended to the pelvic walls. The final result will be a hard bolus the size of a foetal head completely filling the pelvic cavity. A tight binder and firm perineal band are then applied. Anything short of this would be useless. One or two sanitary towels placed in the vagina would be more likely to increase bleeding than to stop it. Vaginal plugging is a serious undertaking; nevertheless it is effective as a first-aid measure to stop the bleeding. It could be employed in special circumstances such as in a ship at sea or in a remote area.

A more readily applicable though short-term first-aid measure that can be used during the hour awaiting the arrival of help is bimanual compression. This has always been taught as a means of controlling post-partum haemorrhage, but many are unaware that ante-partum haemorrhage can be stopped by this means. In the desperate case that would decide the attendant to adopt this procedure an anaesthetic is not given. The operator lubricates his right hand (soap will do), forms it into a cone, and by pronating and supinating inserts the whole hand into the vagina. The vaginal vault will be found readily capacious and there a fist is made. The left hand presses on the fundus uteri and so the uterus is squeezed between the two hands.

Twenty-five years ago, when I was district obstetric officer to the Princess Mary Maternity Hospital, it was my duty to call daily on a woman 36 weeks pregnant who had been allowed home from the hospital after one or two small ante-partum haemorrhages because she lived near the hospital and beds were needed. One morning just as I walked in she began a dangerously profuse loss. I was alone and had no materials with me. Bimanual compression was applied and the attention of the neighbours attracted by kicking on the floor. It was an hour before help and an ambulance arrived, but during the whole of that time the bleeding, which was from central placenta praevia, was fully controlled and the patient arrived at hospital in good condition.

Subsequent Management

What is done for the patient after she arrives in hospital is less a matter for this article than for hospital staffs, but as any one of us may be called on to cope with these patients there are one or two principles that should be laid down. There is little room for definitive treatment between simple rupture of the membranes and caesarean section. A great deal of mismanagement has been occasioned by careless reading of Professor Macafee's admirable article on placenta praevia.* It has been asserted that he was against vaginal examination in cases of ante-partum haemorrhage for fear of inducing bleeding in a patient with placenta praevia. The fact is that Professor Macafee wrote, "A vaginal examination should be made in all cases of suspected placenta praevia," but he emphasized that that examination should never be undertaken anywhere but in hospital, and then only if one is prepared for an immediate caesarean section and that the choosing of the time of this examination is a matter for careful thought. There are few obstetricians who would disagree with these dicta. Another misinterpretation is that conservative treatment of placenta praevia can be carried to the extent of allowing patients with this condition to go home until they are nearer term. Such vagueness is perilous. Macafee restricts this licence decidedly to primigravidae who live near and who have been warned not to permit vaginal examination. It is safest never to allow a woman with any degree of placenta praevia to go home. There is strong evidence that many of the severe haemorrhages in placenta praevia have been precipitated by sexual intercourse.

Simple rupture of the membranes may be employed for placenta praevia type I and for most of type II, or for accidental haemorrhage revealed or mixed. On the other hand, lower segment caesarean section is best suited for placenta praevia types III and IV, and for some of type II in which the placenta is situated posteriorly. These are not clear-cut rules and other factors such as the viability of the child, degree of maturity, and parity may alter the decision. A few cases of concealed accidental haemorrhage may need caesarean section or even caesarean hysterectomy. Bringing down a leg in a breech or transverse lie and permitting spontaneous expulsion are still occasionally employed for either variety of ante-partum haemorrhage, notably in patients who are multigravid and in whom the foetus is dead or so premature that its life is valueless.

J. Obstet. Gynaec. Brit. Emp., 1945, **52**, 313.

Bipolar version, which carries such a high foetal mortality, is now little employed except in multiparae when foetal survival is unlikely, and then usually well before term. In any event it is doubtful whether it achieves anything more than to ensure thorough rupture of the membranes and escape of liquor amnii.

Conclusion

All cases of ante-partum haemorrhage are cases for hospital. Accurate diagnosis should not be attempted unless the patient is in hospital. In some cases restoration of the patient's general condition is advisable before she is sent in. If in doubt err on the side of safety, and call the obstetric emergency service. In grave and severe cases restorative measures should always be taken before an ambulance journey. If help is delayed there are first-aid measures that will stop the bleeding, but they should be used only in special circumstances.

Next article on Emergencies in General Practice.—"Acute Food-poisoning," by Dr. C. Hardwick.

PUBLIC HEALTH AND PREVENTIVE MEDICINE

ROYAL SANITARY INSTITUTE CONGRESS AT BOURNEMOUTH

About 2,500 delegates assembled at the annual health congress of the Royal Sanitary Institute, which was held at Bournemouth from April 26 to 29 under the presidency of the Duke of Wellington, Lord Lieutenant of Hampshire. The congress met in ten sections, and in addition there were five special conferences for different categories of workers in the public health service. Representatives from more than forty other countries attended, among them three professors from Moscow.

In his address from the chair of the congress the DUKE OF WELLINGTON said that although great improvement in hygiene had taken place during the eighty years of the Institute's existence, much still remained to be done. Visitors from Northern Europe were shocked at the open food shops still to be seen in this country. He wondered whether the rising incidence of cancer might be attributed to the enormously increased consumption of sterilized foods and the use in agriculture of chemical fertilizers. He knew that these possibilities were scouted by many eminent authorities, but every medical discovery had found many people who were unwilling to believe in it at first. He also criticized the pollution of rivers by industrial waste. Another outstanding problem concerned feeble-minded old people. A kind of institution between a mental home and an old people's home was wanted; it was one of the most difficult problems of local government.

The problem of the ageing population was also the theme of the presidential address in the Preventive Medicine Section by Dr. ARTHUR MASSEY, chief medical officer to the Ministry of Pensions and National Insurance. But he thought they were now beginning to see this problem in better perspective, and the idea that future workers would have increasing difficulty in supporting their aged community was becoming less insistent than in the recent past.

Training for Public Health

In the Preventive Medicine Section Professor R. H. PARRY (Bristol) called for closer integration of undergraduate medical training with the public health department and the general practitioner, so that the student might learn more about conditions in home, school, and factory. He believed that in time the general practitioner would be able to take over medical responsibilities at the health clinics and work in close association with the public health staff; but there would always remain the need for certain full-time medical officers to be specially trained for other important duties of the health department.

While it was generally agreed that it was better to prevent than to cure, why was it, asked Professor THOMAS MCKEOWN (Birmingham), that when the opportunity was presented, as in the N.H.S., to plan a service on a national scale all the resources were devoted to the treatment of established disease? It was the result of a widespread belief that health depended mainly upon medical services and particularly upon the hospital service. Yet the improvement in health to-day, as compared with the previous century, was due primarily to the fact that people did not become ill rather than to the treatment they received when they were ill. Disease prevention deserved a higher priority than it was given.

Widening Horizons of Preventive Medicine

In their own special conference the medical officers of health discussed the widening horizons of preventive medicine. Dr. A. L. COCHRANE, after describing the work of the pneumoconiosis unit of the Medical Research Council, operating mainly in a Welsh mining area, said that the diseases which were likely to be important in the future were the chronic disabling diseases with a low case-mortality rate, of which rheumatoid arthritis was an example. The long-term programme of preventive medicine was to investigate the causes of these diseases in order to learn what could be done to prevent them. The first step was to measure the disease prevalence, and for this purpose he described how a representative sample of the community might be taken for survey. Then, with the help of different specialists for each disease, the prevalence in a complete population of bronchitis, diabetes, pulmonary disability, and so on could be estimated. Most techniques for this purpose were now sufficiently far advanced to enable medical officers of health to make a start in measuring the prevalence of some of these diseases in their own area.

Dr. J. H. F. BROTHERSTON (London School of Hygiene and Tropical Medicine) said that the care of the elderly sick was in many ways the most challenging problem facing the health service to-day. The question must be considered in triple terms: (1) in clinical terms, because efficient diagnosis and treatment shortened the problem of care, reduced disability, and lessened the strain imposed on the social situation; (2) in terms of prevention, for every success in this direction prolonged the period of the old person's independence; and (3) in terms of the social background. In any foreseeable future there must remain limitations on the availability of hospital beds for old people, and methods must be found of increasing the contribution of the out-patient department by making it an institution which old people could use in comfort. But the general practitioner must always bear the main burden of looking after old people in their homes, and the elderly were becoming an increasing proportion of this responsibility. There was every reason why supporting services should be brought to his aid in the patient's home. Why should the services of physiotherapy, dietetics, social work, and the like be available only if the patient happened to go to hospital? "It is the extent to which the public health services are able to underpin the home situation which will determine the strength of that situation as a place where more extensive clinical care of old people can be carried out."

Noise at Work

One symposium at the Congress was devoted to the subject of noise at work, its effect on auditory acuity and on behaviour. Air Vice-Marshal E. D. D. DICKSON, consultant in otorhinolaryngology to the R.A.F., said that there was no doubt that, in occupations associated with continual exposure to loud noise, hearing impairment would result. In its early stages this impairment was in the little-used higher-pitch range and did not obviously manifest itself as a disability. An ear which had been exposed to intense noise was seriously injured in the organ of Corti. The

primary lesion was in the destruction of the outer hair cells of that organ. The organ might be ruptured and released from the basilar membrane. A sudden loud sound might cause immediate destruction, whereas a continuance of noise might bring about the process gradually. It was generally recognized that noise which exceeded in intensity a level of 90 decibels was responsible for acoustic trauma. The earliest onset of hearing loss would be detected by audiometry and appear as a dip or notch in the hearing range in the region of 4,000 cycles per second.

Air Vice-Marshal Dickson stressed the need for pre-employment evaluation of auditory function. In claims for compensation in respect of hearing impairment the difficulty was to eliminate that portion of the worker's deafness, if any, which was not due to his occupation, so that compensation was not paid for something which the work had not caused. Specifically to identify the acquired loss without pre-employment audiometric examination and careful history was often impossible. Equally difficult was the assessment of that portion of deafness which came with advancing age and its separation from the deafness caused by occupational impairment. On the question of protection against noise he urged that the planning and lay-out of factories from this point of view should receive more attention.

Two research workers from the Medical Research Council contributed to the symposium. One of them, Mr. T. S. LITTLER, suggested various methods for reducing or suppressing noise. The only way of ensuring sound insulation from the noise of aircraft and machinery was by building screening partitions of sufficient mass. Thick and heavy walls were the only effective insulators. Concerning the protection of the ear by earplugs and earcaps, he said that when the ear meatus was fitted with an efficient earplug there was a limit to the amount of noise reduction it produced, because quite an appreciable amount of sound bypassed the plugs and got into the ear through the cartilage of the meatus and the bones of the skull. When the noise hazard was still great, even after the use of a well-fitting plug, further protection could be obtained by the additional use of a noise-excluding pad, earcap, or helmet effectively covering the auricle.

Mr. D. E. BROADBENT, of the Applied Psychology Unit, Cambridge, discussed the effect of noise on behaviour. The result of such investigations as he had undertaken was that noise did not produce dramatic permanent change in mental health or behaviour; there might conceivably be subtle changes difficult to detect, but there was no convincing evidence either way. The question most urgently requiring an answer was whether noise produced temporary effects on work which did not involve hearing. His experiments had led him to the conclusion that noises did cause brief shifts of attention from the work in hand, and that such momentary shifts became more frequent in the presence of a high intensity noise.

Child Psychiatry

Several meetings during the Congress were devoted to maternal and child health, and the section on mental health was concerned with the child. Dr. KENNETH SODDY (Child Guidance Training Centre, London) discussed the promotion of mental health in the very early years, the first steps of the infant in adaptation to environment, the first relationship formations, the first steps in instinct modification. An important thing in the child's development was the formation of substitute relationships, for which home gave him the opportunity, the father to some extent replacing the mother, so that the child no longer entirely depended upon her, and grandparents and others coming into the picture and preparing the child for relationships with teachers and other adults who would figure in his later life. He spoke also of the influence of the nursery school in making the child a sociable being.

The child guidance clinics, when they came into being a quarter of a century ago, were looked upon as denoting a real advance in preventive psychiatry, but, said Dr. F. H. STONE, consultant in child psychiatry to the Royal Hospital for Sick Children, Glasgow, subsequent events had been rather disappointing. It was true that a traditional team of psychiatrist, psychologist, and psychiatric social worker had elucidated a great deal about the aetiology of childhood emotional disorders. But the children who were referred to the clinics were already emotionally disturbed to such a degree that for treatment to be effective it must be intensive and prolonged. The dream of concentrating on very early and minor disorders had evaporated in the face of hard reality.

There was much still to be learned about disturbed parent-child relationships, about the influence of community stress upon inter-family relationships, about the conflict between child-rearing practice as propagated by newspaper articles or radio talks on the one hand and family tradition on the other. Surprisingly little was known about the mutual influences of physical and emotional growth. It was one thing to collect information about incomes, size of family, and so on, and quite another to investigate the personal and intimate feelings and attitudes which were the only available guides to the emotional lives of human beings. Dr. Stone suggested certain ways in which such research might proceed. The psychiatrist and psychiatric social worker should collaborate with the family doctor and health visitor, who were in a strong strategic position for reaching the parents or the parent-substitutes. They were the first-line forces. He also pointed out the need for maturity and sensitivity on the part of those engaging in this work.

Miss ELIZABETH IRVINE (Tavistock Clinic) spoke of the value of staff consultations, not so much because of what was said or done at them, but because of their effect in relieving the anxiety which any professional group was likely to feel in view of the vital responsibilities it carried in the mental health field.

The Health Visitor

Other discussions at the Congress concerned the contribution of processing techniques to the nutritional value of food, child health in the Tropics, and the health and welfare of the office worker. At a conference of health visitors Dr. H. D. CHALKE declared that health visiting was passing through the most important phase in its history. Already there was a noticeable change of attitude in the hospital service, which was using health visitors to an increasing extent. The position, he said, was not so good in the general-practitioner field, where fusion of interests seemed some way off yet and the old vendetta lingered in many places. It was the health visitor herself who could do most to break down old prejudices. A new generation of doctors and health visitors might achieve greater success than the present, and the coming of group practice might alter the picture.

EMPIRE RHEUMATISM COUNCIL

PLANS FOR A MOBILE RESEARCH UNIT

At the annual meeting of the Empire Rheumatism Council at the Royal College of Surgeons on April 27, Dr. W. S. C. COPEMAN, who was re-elected chairman of the Council, announced that it was proposed to establish a mobile field unit for research into aetiological and environmental factors in rheumatic disease. It would probably follow the pattern of the mobile unit being used to study pneumoconiosis among miners. Enlarging on the unit at a subsequent press conference, Dr. Copeman said it would be available for work in any part of the country and in any industrial setting, and possibly later in any part of the Commonwealth. The Council was prepared to put down £30,000 to complete the project, but support would also be needed from industry, which stood directly to benefit from the research. The running cost would be about £7,000 a year. The team would consist of a medical director, a radiographer, and a social worker, and the backing of a university department would be needed; probably Manchester would be asked to provide this. A medical director for the unit was now being sought. The unit would investigate any

kind of rheumatism, but it was thought that a start should be made with osteoarthritis, which was so widespread in industry.

Other Activities

Referring to the Chair of Rheumatology at Manchester University, which the Council had largely financed, Dr. Copeman said that the Nuffield Foundation had offered the University a further grant of £70,000 to develop research in rheumatism, thus providing the professor with the assurance of a well-endowed department. Two E.R.C. Fellows were at work—Dr. Norymberski at Sheffield, who was engaged in research on steroid chemistry, and Miss Muir at St. Mary's Hospital, Paddington, who was studying connective tissue polysaccharides. The Council had also decided to continue to support Dr. E. Wittkower's study at McGill University of rheumatoid arthritis in two contrasting communities. Dr. Copeman added that he himself had been invited to visit Australia in the autumn to help reorganize the Australian Rheumatism Council, and he had also been invited by the Minister of Health of the Dominion to visit New Zealand.

Mr. W. R. C. HALPIN, chairman of the Finance Committee of the Council, said that the total income for the year, exclusive of legacies, amounted to £19,091, compared with £13,775 in the previous year, and legacies had increased by over £3,000.

GENERAL ELECTION

MEDICAL CANDIDATES

On April 15 it was announced that a General Election would be held on May 26. At the last General Election, in 1951, 14 medical men and women stood as candidates and 10 were elected, the same number as in 1950. According to the information at present obtainable the following 14 members of the medical profession will be standing for Parliament at the forthcoming General Election.

The names of those who were Members of the last Parliament are indicated by an asterisk. It is not possible in all cases to give the age of the candidate, but the year of their qualification affords some guidance, and this has been given in parentheses.

*REGINALD FREDERICK BRITTAIN BENNETT, V.R.D., Gosport and Fareham, Conservative. (1937.)

M.P. for Gosport and Fareham since February, 1950; Parliamentary Private Secretary to the Home Secretary, 1951–4, and to the Minister of Fuel and Power since November, 1954; secretary of the Conservative Parliamentary Committees on Air and Civil Aviation since 1951; psychiatrist to the Institute for the Study and Treatment of Delinquency since 1950; member of the South-west Metropolitan Regional Hospital Board since 1953; member of Steeering Committee of Parliamentary and Scientific Committee, 1952–4; member, Inner Temple; surgeon lieutenant-commander, R.N.V.R.

*ALFRED DAVIES DEVONSHER BROUGHTON, Batley and Morley, Labour. (1929.)

M.P. for Batley and Morley since February, 1949; medical practitioner at Batley, 1932–40 and 1945–50; member of Batley Borough Council, 1946–9; former chairman of Dewsbury Division of B.M.A.; squadron leader, R.A.F.V.R.

*Rt. Hon. WALTER ELLIOT ELLIOT, P.C., *M.C.*, Kelvingrove, Glasgow, Conservative. (1913.)

M.P. for Lanark, 1918–23; Kelvingrove, 1924–5; Scottish Universities, 1946–50; and Kelvingrove since 1950; Minister of Health, 1938–40; previously Secretary of State for Scotland and Minister of Agriculture; rector of Aberdeen University, 1933–6, and of Glasgow University, 1946–50.

*SOMERVILLE HASTINGS, Barking, Labour. (1902.)

M.P. for Reading, 1923–4 and 1929–31, and for Barking since 1945. Consulting surgeon and lecturer to ear and throat department, Middlesex Hospital; member of the North-east Metropolitan Regional Hospital Board; Past President, Socialist Medical Association; member of London County Council for Mile End, 1932–46; chairman of Hospitals and Medical Services Committee of L.C.C., 1934–44; chairman of London County Council, 1944–5.

*Rt. Hon. CHARLES HILL, P.C., Luton, Liberal and Conservative. (1927.)

M.P. for Luton since February, 1950; Parliamentary Secretary to the Ministry of Food, 1951–5; Postmaster-General since April 7 this year; Secretary, British Medical Association, 1944–50; President, World Medical Association, 1949–50; vice-president, and formerly chairman, Central Council for Health Education.

BERNARD HOMA, Hendon South, Labour. (1922.)

In general practice. Member of London County Council for over 20 years; member of board of governors of Charing Cross Hospital.

DONALD MCINTOSH JOHNSON, Carlisle, Conservative. (1926.)

Contested Chippenham Division of Wiltshire as a Liberal at the General Election in July, 1945; medical officer with East Greenland expedition in 1926 and, later, medical officer in Grenfell Mission to Labrador; left general practice to serve in the R.A.M.C. in the second world war; since founded publishing firm; member of Sutton and Cheam Borough Council.

ROBERT DOUGLAS MCINTYRE, Perth and East Perthshire, Perthshire and Kinross-shire, Scottish Nationalist. (1938.)

M.P. for Motherwell and Wishaw, April–July, 1945; chairman, Scottish National Party, consultant chest physician and supervising tuberculosis physician, Stirlingshire and Clackmannan since 1948.

CATHERINE EDITH ORR-EWING, Bermondsey, Conservative. (1926.)

Senior hospital medical officer, Royal Eye Hospital; school ophthalmologist, Southall, Heston, and Isleworth.

DOUGLAS RENE LOUIS MARCEL POIRIER, Louth, Lincolnshire, Labour. (1943.)

In general practice at Winterton, near Scunthorpe; appointed factory doctor; medical officer under the Ministry of Pensions and National Insurance.

FRANCIS REGINALD ROBERTS, Walsall, North, Conservative. (1928.)

In general practice; member since 1940, and chairman in 1949–50, Brownhills Urban District Council, and chairman of health committee for many years; recently elected to Staffordshire County Council.

*MALCOLM STODDART-SCOTT, O.B.E., T.D., Ripon, West Riding, Conservative. (1926.)

M.P. for Pudsey and Otley, 1945–50, and for Ripon since February, 1950; chairman of British Group of the Inter-Parliamentary Union since 1951; on medical staff of General Infirmary at Leeds, 1929–39; A.D.M.S., 48th Division, 1943–5; chairman, British Rheumatic Association.

*BARNET STROSS, Stoke-on-Trent Central, Labour. (1925.)

M.P. for Hanley Division of Stoke-on-Trent, 1945–50, and Central Division since 1950; formerly in general practice at Stoke-on-Trent.

*Rt. Hon. EDITH CLARA SUMMERSKILL, P.C., Warrington, Labour. (1924.)

M.P. for Fulham West since 1938; Parliamentary Secretary to the Ministry of Food, 1945–50; Minister of National Insurance, 1950–1; Chairman of Labour Party since September, 1954.

The Medical Sickness, Annuity and Life Assurance Society, Ltd., celebrated its recent move into larger premises at No. 3, Cavendish Square, by holding a reception there on April 26. Mr. R. J. MCNEILL LOVE and Sir CECIL WAKELEY, the chairman and vice-chairman of the Society, received the guests. The new offices are needed to cope with the expanding business of the Society, which now has a membership of over 15,000 doctors and dentists.

HEALTH AND POLITICS

The Conservative Party's general election manifesto[1] contains a section entitled "Home and Family," and the following appears under the heading "Good Health":

New hospital building was completely neglected by the Socialist Government. A start is now being made. Plans have been announced and will be carried out over the next few years for the building of new hospitals, both general and mental, and for the extension and modernization of many existing hospitals. We are making special arrangements to replace worn out and obsolete hospital plant and equipment. We shall seek to open new beds where they are most needed, to recruit extra staff and to provide better facilities. We desire to see steady progress in all forms of preventive work. These are our priorities: we rank them higher than free wigs or free aspirins.

We believe that private practice and contributory schemes have a part to play with the National Health Service and we shall therefore maintain the system of hospital amenity and hospital pay beds. We have cut away restrictions on voluntary effort in the hospital service. We shall continue to give every encouragement to voluntary work.

We welcome the increase in the provision of dental treatment, especially for mothers, children and young people, and we wish in co-operation with the profession to push forward with preventive measures.

The problems of the elderly must concern us all. In particular we shall encourage local health authorities to build up their home help services and to provide "half-way houses" for the old.

We shall introduce legislation to give effective status to those, known as medical auxiliaries, who assist doctors in investigation and treatment.

We are anxious to provide the best National Health Service the country can afford. We set up the Guillebaud Committee to study the problems involved and await its recommendations.

The steady fall in infant and maternal mortality rates is a wonderful measure of the nation's better health. Quarter by quarter the records are being broken. We are winning the fight against tuberculosis. Still a great challenge remains for all concerned with the prevention and cure of disease. We shall make sure that adequate funds are available for medical research, and in particular that hopeful lines of inquiry into cancer and polio are urgently pursued.

Air pollution is an enemy to good health, and can cause death. We wholeheartedly accept the need for a national "clean air" policy. The use of smokeless fuels must be encouraged wherever they can readily be made available, and comprehensive legislation on smoke abatement will be introduced.

The section in the Labour Party's manifesto[2] about "Helping the Family" include the following paragraphs under the heading "Health and Old Age."

Through the National Health Service and National Insurance, the Labour Government began to abolish the fear of old age, sickness and disablement which haunted working-class life before the war. We shall go forward with the job.

In order to restore a free Health Service, we shall abolish all charges, including those on teeth, spectacles and prescriptions. We shall stop queue-jumping by ensuring that the need for treatment and not ability to pay shall be the test for obtaining a bed in National Health Service hospitals.

Now social security must be carried one stage further. In order to remove the last taint of "public assistance," a Ministry of Social Welfare will be established to take over the work not only of the Ministry of Pensions and National Insurance, but also of the National Assistance Board.

To maintain the real purchasing power of these benefits, pensions and allowances, we shall institute an annual review, and in any year in which there has been an increase in the cost of living, the scale of payments will be increased accordingly.

One of the first acts of the next Labour Government will be to improve the rates of National Assistance fixed last February by the Tory Government, an increase which we regard as quite inadequate. We shall also deal with the anomalies of the National Insurance and Industrial Injuries schemes.

Also in the Labour Party's manifesto are promises to enforce clean food standards in shops and restaurants, and greatly to extend water supplies and bring them under public ownership.

[1] *"United for Peace and Progress": The Conservative and Unionist Party's Policy, General Election, 1955.*
[2] *"Forward with Labour": Labour's Policy for the Consideration of the Nation, 1955.*

IMPERIAL CANCER RESEARCH FUND

The 16th annual general meeting of the governors of the Imperial Cancer Research Fund was held at the Royal College of Surgeons on April 28, with Professor H. R. DEAN, chairman of the Council, in the chair. In presenting the annual report, which chiefly summarized the work of the central (Mill Hill) laboratory and the clinico-pathological laboratories at Lincoln's Inn Fields, Professor Dean said that the histo-pathological resources had been considerably augmented during the past year, and numerous minor alterations had been carried out and equipment added to facilitate the scientific work. Cancer research had grown to include every branch of chemistry and biology. As the report stated, a few years ago the Fund decided to open another laboratory for clinico-pathological studies, and for this the Royal College of Surgeons offered facilities and members of the staffs of London hospitals gave their assistance. An offer from the Royal College for the use of two adjacent sites in Lincoln's Inn Fields had been accepted, and as soon as the College was able to vacate these buildings—probably in the latter half of next year—the sites would be let to the Fund on a 99 years' lease, with the right to demolish the existing houses and rebuild in such a way as would give the clinico-pathological unit greatly increased space.

Latent Cancer

Professor Dean went on to say that it had long been known that the growth of cancer was not continuous, but that intervals might occur during which the tumour remained dormant, sometimes for many years, after which it resumed an active progress often terminating fatally. Recent research had shown that cancers might arise within the human body so small as to cause no symptoms or inconvenience, remaining dormant throughout the life of the individual. Of 220 men who had died from various causes, and whose organs were examined after death by Dr. L. M. Franks, a member of the scientific staff of the Fund, microscopic evidence of cancer of the prostate was found in 36%, and yet in all these cases the local and general effects associated with the presence of cancer were absent. Few were found in men under 50 years of age; with men in the sixties and seventies the tumours were found in about one-third of all cases; in men over 70 in nearly half; in men over 80 in three-quarters; and in nonagenarians in practically all cases. An investigation of latent cancer in other organs was being carried out by Dr. Franks and Dr. F. C. Chesterman in the thyroid, and by Dr. J. Stretton Young in the breast. The work involved a thorough survey of these organs and the use of large sections. A similar problem, investigated by Dr. J. Bamforth, concerned the relationship between hyperplasia of the endometrium and the occurrence of cancer in the uterine body. Dr. E. F. Scowen and his surgical colleagues at St. Bartholomew's Hospital, with the help of the Fund's laboratories, were making a combined clinico-pathological investigation into the human "soil" in which breast cancer flourishes.

Speaking of the work of Dr. James Craigie, director of the central laboratories, on the preservation of tumours by freezing, Professor Dean said that this allowed further study to be made of these tumours after months or years, and their comparison with other tumours. This work had shown that there were two distinct types of cells concerned in carcinoma. The investigations now in progress in the laboratories, varied as their objectives might appear, and varied as were the methods employed, were all in fact closely related to the advancement of knowledge of the cause, progress, and consequence of cancer.

Financial Position

The accounts of the Fund, presented by Mr. DICKSON WRIGHT, the honorary treasurer, showed an improvement in income from all sources, and the number of subscribers to

the Fund had again been much increased. The expenditure for the first time had exceeded £100,000, of which total only £6,582 had been spent on administration and £6,436 on publicity. The number of full-time people employed in the service of the Fund was eighty, and expenditure was always rising. The public had always been conscious of the claim that cancer research made upon their purses and the need for bringing nearer the day when the cause and cure of cancer were discovered.

Viscount Halifax was re-elected President of the Fund, and Mr. Dickson Wright treasurer. The two retiring governors, Lord Amulree and Sir Henry Dale, were re-elected, and the following were approved as "appointed members" of the Council representing the branch of science indicated: Professor H. R. Dean (pathology), Sir Charles Lovatt Evans (physiology), Dr. Cuthbert Dukes (pathology), and Sir Cecil Wakeley (surgery). A vote of thanks to the Chairman was moved by Sir Arthur MacNalty.

Reports of Societies

OUTLOOK FOR THE HYDROCEPHALIC INFANT

"Hydrocephalus of Infancy" was discussed at a meeting of the Paediatric Section of the Royal Society of Medicine on March 30, to which were invited members of the Section of Neurology.

Importance of Early Recognition

Dr. HUGH JOLLY (Plymouth) defined the subject of the meeting as internal hydrocephalus affecting children in the first year of life. Its incidence, he said, seemed to be about 0.2%. It was somewhat commoner among boys than girls, and increasing age of the mother made greater the risk of a child being hydrocephalic. Early diagnosis was essential. Hydrocephalus was suggested by a large globular head with relatively small features, in distinction to the flat top and relatively large features of a child with a large, but not hydrocephalic, head. The latter condition was sometimes familial. The size of the fontanelle was of little value in diagnosis, but a raised tension was of great importance. The eyes characteristically turned downwards in developing hydrocephalus, and might become central after tapping the ventricles. Irritability, spasticity, and decerebrate rigidity were terminal signs, continued Dr. Jolly, and papilloedema was not a feature, except in those cases where the hydrocephalus had been caused by a tumour. Loss of intelligence varied with loss of brain substance.

Investigations should include a radiograph of the skull to rule out intracranial calcification due to toxoplasmosis; routine examination of the cerebrospinal fluid, including a Wassermann reaction; and bilateral subdural taps to exclude subdural haematoma. These should be followed by a dye test, using indigo-carmine, to establish the site of obstruction, and by ventricular air studies, using not more than 50 ml. of air.

The choice of patient for treatment was determined by obvious lack of spontaneous arrest. Poor intellect was not necessarily a contraindication to operation, especially as the degree of attainable intelligence was most difficult to determine. Measurement of the thickness of the cerebral cortex provided some guide to this, and if it was less than 1 cm. mental deficiency was certain. The operation of lumbar arachnoid-peritoneostomy, as performed by Spitz, of Philadelphia, had been used successfully in Plymouth on three out of four recent cases by his surgical colleagues.

Dr. Jolly ended with a plea for more clinical research on hydrocephalus. Little was known of the natural history of the condition, and it was still impossible to forecast those cases which were likely to undergo spontaneous arrest. In view of the fact that the condition was less often fatal than commonly believed, he felt that more cases should be offered surgery and that many of the children so treated would have an improved mentality, even if they could not become altogether normal.

Increased Formation of C.S.F. an Unlikely Cause

Professor DOROTHY RUSSELL (London) opened her communication by recapitulating the principal obstructive lesions that may be responsible for hydrocephalus in infancy. She criticized the hypothesis that increased formation of cerebrospinal fluid is a cause of this condition. In recent years it had been suggested that both vitamin-A deficiency and hypervitaminosis A produced hydrocephalus in this way. The repeated injection of trypan blue into female rats during pregnancy had a similar effect upon the offspring. The mechanism in these forms of disease had yet to be demonstrated.

The production of hydrocephalus from impaired absorption of cerebrospinal fluid remained a problem, went on Professor Russell. Sinus thrombosis might be associated with a variety of cerebral complications, and the factors responsible for these required further clinical investigation.

Results of Surgery

Mr. GEORGE MACNAB (London), the president of the Section of Paediatrics, discussed observations he had made during the study of 160 infants with hydrocephalus, of whom 105 had been submitted to operation. The first point in the distinction between an infant with a large head and one with hydrocephalus was the turning down of the eyes in progressive hydrocephalus; the eyes returned to the natural position when the hydrocephalus was arrested. The second point was that clinical estimation of tension in the anterior fontanelle as a sign of progressive hydrocephalus was unreliable. Tension was not clinically recognizable until the ventricular pressure in the horizontal position was around 250 mm., yet many cases of progressive hydrocephalus with rapid enlargement of the head had pressures of only 110 to 180 mm. The ventricular pressure ranged between 50 and 180 mm. where there was free communication between ventricular and spinal fluid, compared with pressures of 250 to 300 mm. in cases of intraventricular block.

In progressive hydrocephalus, continued Mr. Macnab, the average increase in the size of the head in the first three months of life was 3 in. (7.6 cm.); a similar increase was seen in the size of the head of a 30-week premature baby, as compared with an increase of 1.2 in. (3. cm.) in the normal full-term infant. In his series papilloedema was not seen, although excessive pallor of the disks was always present. Blindness, however, was a sudden and terminal event, and did not occur early.

A small group of cases had large, flat-topped heads and a wide anterior fontanelle. Air encephalograms showed air passing over the cortex and some dilatation of the ventricular system, with a ventricular pressure as high as 240 mm. These cases were probably due to a relative impairment of absorption, balance occurring at a higher pressure level than normal.

Out of the whole series 57 of the 160 cases became arrested. Five of these were of the type with a flat top to the head; 19 underwent natural arrest, and 33 following operative procedures.

Forty out of the 160 cases were due to the Arnold–Chiari malformation. Dr. A. H. Cameron had shown, said Mr. Macnab, that hydrocephalus at birth in association with the Arnold–Chiari malformation might be due to obstruction at the aqueduct of Sylvius or at the foramina of Magendie and Luschka, and that the cerebellum might obstruct the cerebrospinal fluid circulation by herniation through the tentorial notch. Dr. Cameron had also shown that venous congestion over the malformation might be followed by arachnoiditis leading to the late development of hydrocephalus.

Operative Procedures

Various operative procedures had been used in the 105 cases, went on Mr. Macnab, beginning in 1929 with bilateral ligation of the common carotid arteries with the object of reducing the rate of C.S.F. secretion. Neither this nor diathermy of the choroid plexuses caused any improvement. McNickle's blind third ventriculostomy for aqueduct stenosis had proved unsatisfactory, as had also a similar open operation. Ventriculo-pharyngostomy, by the insertion of a polythene tube into the temporal horn of the lateral ventricle and drainage into the aditus of the mastoid antrum, produced arrest in six out of fifteen cases, but eight cases had died some months after operation.

In lumbar myelomeningocele, drainage of the sac into the peritoneal cavity through a polythene tube was unsuccessful because of loculation inside the sac. A polythene tube passed into the spinal canal above the sac and threaded into the ureter produced some variation in tension in the sac, but two cases had died in uraemia some months after operation. A modification in which the kidney was removed and the polythene tube passed direct into the ureter allowed drainage to take place when the cerebrospinal pressure was high, but eventually blockage or reflux infection occurred.

Drainage by polythene tube from the temporal horn of the lateral ventricle into the transverse sinus had proved unsuccessful in most of the cases so treated, as had also drainage of the ventricle into the peritoneal cavity or the ureter.

New Drainage Device

The current method of treatment, said Mr. Macnab, was drainage of the lateral ventricle directly into the subarachnoid space by the use of a double nylon disk lying in the subarachnoid space. From the disk led a tube which coiled into a spiral after its introduction into the ventricle. This apparatus had been devised by Mr. D. M. Forrest, registrar at the Westminster Children's Hospital. Sixteen cases had been operated on, and at the end of three months they showed a big drop in ventricular pressure, but two post-meningitic cases were not arrested.

In the discussion which followed, Dr. J. E. SCARFF (New York) said that he thought that tension of the anterior fontanelle was the most useful sign of developing hydrocephalus. If there was no obstruction the level of the fontanelle should slowly fall if the child were held up by supporting it under the armpits. In respect to surgical measures, he was using the operation of opening the floor of the third ventricle, as described by Dandy; out of 34 cases 15% had died at operation, in 30% the operative results were unsatisfactory, and 54% had returned to normal.

Mr. A. N. GUTHKELCH (Manchester) said that he had seen 160 cases in seven years. He had operated upon 90. Twenty were too severe, 20 too mild, and 30 (all associated with myelomeningocele) were complicated by complete paraplegia. In cases of internal obstruction, especially anomalies of the iter of Sylvius, he had used Torkildsen's operation for draining the ventricle into the cisterna magna with good results. In communicating hydrocephalus he had had 12 successes for periods of up to 18 months with spino-peritoneal drainage. Spino-ureteric drainage had been as successful in relieving pressure, but there was a morbidity from chloride loss and urinary infection.

Mr. DENIS BROWNE (London) discussed his theory of the production of the Arnold-Chiari malformation by intra-uterine compression.

Mr. D. M. FORREST (London) then demonstrated the disk he had devised and which was being used by Mr. Macnab for draining the ventricle.

Necropsy Evidence

Dr. A. H. CAMERON (Sheffield) described his necropsy findings on 42 cases of hydrocephalus, of which 23 had been investigated at the Hospital for Sick Children, Great Ormond Street, whilst he was Hydrocephalus Research Fellow there. Post-inflammatory stenosis of the aqueduct was present in seven cases with spina bifida, four cases of post-haemorrhagic hydrocephalus, and two cases of meningo-encephalitis. Congenital stenosis was present in one case with spina bifida and one case with encephalocele. Forking was present in five cases, all with spina bifida; in two of these there was superadded inflammatory stenosis, and in one of the other three the aqueduct, though forked, was not abnormally narrow. Congenital stenosis or forking was not found in any of the cases without spina bifida or encephalocele.

There was conclusive evidence that the spina bifida lesion was in each case a myelocele. In the six neonatal cases dying within two weeks of birth the cord tissue presented on the surface of the sac as an unclosed neural groove; this was covered over by fibrogranulation tissue in the four cases dying within the first two months of life; and in the remainder it was in much the same superficial position but covered over by fibrous scar-tissue and squamous epithelium. In the cases of spina bifida there was a high incidence of diastematomyelia, rib deformities, deformities of the vertebral column underlying the sac and at higher levels, and of congenital abnormalities of the urogenital tract. This was considered to be the result of inhibition of Hensen's node during early embryonic life. Attention was drawn to the similarities between spina bifida in the human and experimentally induced spina bifida in amphibia.

Three cases of duodenal ulceration, all with gross internal haemorrhage, were encountered. In each case there was a suppurative inflammation of the meninges and ventricular lining involving the attenuated floor of the third ventricle. This was considered to support the neurogenic hypothesis developed by Harvey Cushing.

LOCAL MEDICAL SOCIETIES

Devon and Exeter Medico-Chirurgical Society

It was salutary to remember that doctors were unnecessary, said Dr. FFRANGCON ROBERTS when addressing the Devon and Exeter Medico-Chirurgical Society on April 14. He was speaking on the historical relation between preventive and curative medicine. Many civilizations had flourished without doctors, he said. What had influenced population growth was not medical progress but food and epidemics. Since 1801 the population of Britain had increased fivefold, and thirty-fold since Domesday. From the dim past to the nineteenth century the birth rate had been high, about 35–40 per thousand, but the death rate was only slightly lower, so that only two children per family could be expected to survive. In the fifteenth century the towns became graveyards, and the country areas only a little less so. The Great Plague was not much greater than some previous epidemics; for some obscure reason it was the last. London's population was constantly recruited from the country, but had the plague victims remained in the country they would have died, just as inevitably, of starvation. Eighteenth-century enterprise caused the growth of towns, more food production, and increased population. But sanitation was still bad. Civil engineering was not understood and Roman teaching had been forgotten. The fall in the death rate from 35 per thousand in 1750 to 20.5 in 1815 was not due to medical progress. Vaccination and improved midwifery—due to the decline in rickets owing to better feeding as much as to Smellie's work—were the only purely medical factors contributing to this improvement. Much more was it due to increased cleanliness and sobriety. The industrial revolution was accompanied by an agricultural revolution as a result of which beasts could be fattened and kept throughout the year and winter milk became available. Only recently had curative medicine begun to reinforce preventive medicine, thus creating an entirely new kind of civilization in which, medically speaking, the individual had come into his own. Living longer, he experienced more diseases, many of which required expensive investigation and treatment; hence the great and increasing cost of the Health Service, which must be paid for by the labours of the community, not assumed as a right or a gift from heaven.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Youth Looks at General Practice

SIR,—The article "Youth Looks at General Practice," by Dr. C. P. D. Grant (*Journal*, April 30, p. 1049), should be read by every medical practitioner and senior medical student, for it expresses the views of the majority of young general practitioners. In a short space Dr. Grant reviews comprehensively the fears, problems, hopes, and subsequent thrill of success that result from the efforts of the general practitioner. I should like to stress several of his points and elaborate them.

It is true that many of us on qualifying set as our ideal a specialty and rather unwillingly later turn to general practice as the permanent sphere of our work. Having arrived in general practice it is found that we are lacking in many of the essentials which are necessary to make a success of the job. We do not know what measles is like, and have never seen a patient suffering from diphtheria. In fact, many of us have never even seen a sore throat; and we certainly have never tried to treat one before. Neither do we appreciate the differences in approach which are necessary in the surgery and home, as compared to the hospital. We have not access to white cell counts and endless *x*-rays to aid our diagnosis. We have to diagnose perforated ulcers immediately after perforation and not six hours later, as the hospital staff can do.

These defects show a grave lack of foresight in our medical education which is partly administrative and partly due to the teaching clinician. Those who arrange our curriculum and timetables have not yet fully appreciated the ever-widening gulf between hospital practice and general practice, which has become so pronounced since the end of the war. Our teaching clinicians are composed more and more of younger men who, though brilliant in their own sphere, have little, if any, personal experience of general practice. As a result, they do not know what the medical student needs to be taught. The uses of cortisone and intravenous terramycin are of no great importance to the general practitioner; but which student has been taught how to treat influenza?

Learning the job takes time, but if we are willing and humble a great deal can be learnt quickly. Like Dr. Grant, I have had to learn to try to control a temper which I had not realized existed. But we must learn to endure fools; and also eccentric hospital consultants. There are consultants who will only do domiciliary visits on a Sunday afternoon, and those who will not do them outside a town except under pressure. These are in a minority, granted, but one cannot always do without their services. The majority fortunately are on extremely good terms with the general practitioner and are only too willing to help at any time.

The greatest satisfaction comes from being accepted as a family doctor, and as such I consider it is my duty to provide full maternity services to all my patients who request such services; and the majority prefer their own doctor to the clinics. I am glad we have no regulation in force in this part of the world like there is in Glasgow controlling admission to maternity beds. Here the general practitioner has equal access to beds as do the local authority clinics and those who attend the hospital clinics entirely. It seems to me that the local authority clinics for maternity care have largely outworn their usefulness in many areas, and could be dispensed with or curtailed. As Dr. Grant says, it is the general practitioner who has to deal with the antenatal emergencies, and not the clinic.

Finally, let us realize that the patients themselves are mostly considerate and appreciative, often out of all proportion to the services rendered to them. But a word of advice to those who have not yet settled in practice—get out of the seaside resorts and wealthy residential areas, and practise in an honest-to-goodness working-class area, where there is more work, more appreciation, and more satisfaction to be gained.—I am, etc.,

Rossington, Doncaster. G. F. G. MARSHALL.

Clinical Staging of Cancer of the Breast

SIR,—Mr. Michael Harmer's letter (*Journal*, March 26, p. 790) is timely in calling attention to the need for a method of staging breast cancer which is recognized internationally. Many methods of treatment are now being practised, and it is therefore important to be able to compare the results from different centres. At present, there are at least ten different methods of staging the disease, which makes a comparison between results difficult and often impossible, and has prevented a proper evaluation of some of the results published in the past. The need for an international method of staging breast cancer such as exists for cancer of the cervix is well recognized, and the problem of finding a method acceptable to the majority of workers has already been discussed at several cancer congresses. If a simple method of staging cannot be agreed upon, it would still be possible to present the results in such a way as to enable the work of different centres to be compared.

The features which influence the prognosis and on which most methods of staging are based are the fixation of the primary tumour to skin, pectoralis major, and chest wall; the presence of enlarged axillary nodes and their fixation; the presence of supraclavicular nodes and distant metastases. Cases would be placed into various groups according to which of these structures was involved at the first clinical examination. If distant metastases were present, however, further subgrouping according to the local condition of the primary tumour would seem unnecessary. In the same way, one group would suffice for cases having supraclavicular node involvement and one group for cases with fixed axillary nodes. For the less advanced disease, a number of groups would be required, depending on the state of the primary tumour and the axillary nodes. For example, a suggested arrangement of groups might be:

Visceral Metastases Present:
Group A.

No Visceral Metastases, Supraclavicular Nodes Present:
Group B.

No Visceral Metastases, no Supraclavicular Nodes:

Group C.	Fixed axillary nodes.	
Group D.	Mobile axillary nodes	—primary fixed to chest wall.
Group E.	" " "	—primary fixed to pectoralis major.
Group F.	" " "	—primary fixed to skin.
Group G.	" " "	—primary mobile.
Group H.	No axillary nodes	—primary fixed to chest wall.
Group I.	" " "	—primary fixed to pectoralis major.
Group J.	" " "	—primary fixed to skin.
Group K.	" " "	—primary mobile.

Other groups might have to be added to include certain clinical features considered to be of importance in prognosis such as overlying skin nodules, *peau d'orange*, etc. Of necessity, the number of groups would be rather large and this would mean that only a few cases would be included in some groups. When results were being compared, however, it is likely that several groups would be considered together, and the small numbers in some groups would therefore not be a disadvantage. Individual groups could be rearranged according to any method of staging, and it would thus be possible not only to compare the results published by different workers but also to make a comparison with previously published figures where the method of staging was known.—I am, etc.,

London, W.12. ROBERT MORRISON.

Carcinoma of Bronchus and Pulmonary Tuberculosis

SIR,—I was very interested to read Dr. A. Sakula's article (*Journal*, March 26, p. 759) on this subject. He is quite right in stating that this combined condition is not uncommon. During the years 1951–4 I have seen nine cases, all male, occurring in Birkenhead and Wallasey—a total population of 244,000—in which the adult male pulmonary cases on the tuberculosis register at the end of the four years in question were: 1951, 985; 1952, 937; 1953, 1,027; 1954, 1,115; and the cases of carcinoma occurring in the lung in men were: 1951, 43; 1952, 50; 1953, 49; 1954, 54. I realize that the total number of cases involved cannot possibly be statistically significant, but I feel that these background figures are worth recording.

In addition to these cases, I have seen two other cases during this period in which it was quite likely that the same two conditions coexisted, but the proof is not sufficient to record them as definite. All but one of the cases have been proved histologically or by post-mortem examination, and in the other the *x*-ray and clinical evidence was such as to make the diagnosis certain. Two cases did not show any tubercle bacilli in the sputum, but the laryngeal biopsy in one and the tuberculous epididymo-orchitis in the other indicated that the infiltration in the lungs was definitely tuberculous. I have not the exact details of the smoking habits of all the patients, but they all certainly smoked, and at least four of them were heavy smokers. The site of the carcinoma did not appear to be related in any way to the site of the tuberculosis. In six cases the carcinoma appeared to supervene on established pulmonary tuberculosis, while in three others the two conditions appeared to occur more or less simultaneously.

As we go on keeping our patients with active pulmonary tuberculosis alive, so, I think, we must be on the constant look out for a carcinoma supervening on the pulmonary tuberculosis, though many cases seem to be the sort in which it is unlikely there will be much in the way of successful treatment, partly because of their age and partly because of the rather extensive nature of the tuberculosis. If one of my cases had been diagnosed earlier, he might possibly have been treatable by pneumonectomy, and so I think it is important that we should bear the combined diagnosis in mind should a case of pulmonary tuberculosis fail to respond to treatment within the first three months. The other important point is that any small rounded nodule appearing in routine serial *x*-ray follow-up of patients with pulmonary tuberculosis should be regarded as a potential carcinoma, and, should the local chest condition permit it, early resection should be seriously considered.

I should like to acknowledge the help of the pathologists who carried out the post-mortem and histological examinations; of Mr. Ronald Edwards, who carried out the bronchoscopies; and of Dr. Fulton, medical director of the Liverpool Radium Institute, who supplied the figures for the incidence of carcinoma of the lung in the area.—I am, etc.,

Liverpool, 1. DAVID L. CALDWELL.

Natural Childbirth

SIR,—Although at one time I was an ardent follower of Dr. Dick Read I came to feel that for a function that was meant to be "natural" elaborate instruction and exercises in class twice a week and alone twice a day seemed unnecessary. I developed a routine in practice that seemed satisfactory. At the first visit I gave a little explanatory talk on pregnancy and labour accompanied by diagrams on the blotter, and explained a simple exercise for the abdominal muscles (this is more diligently practised if it is explained that it will help the figure return to normal after the baby arrives). At about 36 weeks I gave a slightly more detailed description of labour and the gas and air machine. I tried to be present very early in labour to show the woman how to put into practice what I had told her about relaxing. I then visited her frequently to keep up her morale, and towards the end of the first stage stayed. Relaxation achieved in this way is just as good as that much practised beforehand, and apprehension is less. After labour I gave further exercises for the abdominal muscles and for the perineum. I have never used exercises designed to increase pelvic capacity during pregnancy. They may add to the prevalent low backache due to sacro-iliac strain.

It is a mistake to tell a primipara that labour should be painless. In animals, where it is all perfectly natural, first labours appear to be accompanied by considerable pain (cats and cows). With complete relaxation I fail to see why the end of the first stage should be painful, as your correspondents seem to think. I personally have never found it so, but I think the final stretching of the perineum as the head crowns with a first baby is nearly always painful. It is for this that the gas and air is invaluable. It need not cause lack of co-ordination with subsequent loss of control as stated by Mrs. Alison Duddington (*Journal*, April 16, p. 971). It will do this if it is not started till the woman is distressed and not in a mood to use it calmly. She should be taught to use it in the painless contractions at the beginning of the second stage; it will then prove invaluable both to the woman in relief from pain and to the attendant in increased co-operation from a calm patient at the end. When properly used it causes no clouding of consciousness.

One thing that is not fully realized is that this type of instruction can only be given to patients willing to receive it. The majority of women are much too shy of these matters to attend classes or even tolerate private instruction. They prefer to keep it all wrapped up in mystery and old wives' tales. The beginning of a first pregnancy is the wrong time to radically alter an outlook, and most women will not take kindly to a doctor who tramples on her prejudices at this time. Much might be done by health education to change the attitude of young people before they start on their families.—I am, etc.,

Wednesbury. HAZEL B. BAKER.

SIR,—As another doctor's wife whose 3-weeks-old daughter was born in hospital, I should like to comment upon Mrs. Constance Lynn's letter (*Journal*, April 2, p. 851). While in the maternity ward I was struck by the great difference in behaviour and attitude of mind between the mothers who had attended classes and those who hadn't, and which affected at least the first part of their labour. I remember in particular one woman who confided in me her absolute dread of being wheeled to the labour ward—she lay in bed tense with fear and not through the pain of contractions. I thought then that if only she had attended the voluntary lectures and classes and visited the labour ward she would have realized there was nothing to be afraid of. Was it only coincidence, I wonder, that eventually she had a caesarean section, as labour was not progressing satisfactorily?

I am sure, however, that understanding the natural process of labour is as beneficial as exercises and relaxation. A woman is much more likely to remain co-operative—particularly towards the end of the first stage when relaxation is very hard—if she understands what is happening. As to my own application of exercises and relaxation, I did find the latter helpful, although I found it impossible to maintain complete relaxation towards the end of the first stage.—I am, etc.,

London, S.W.11. RACHEL LITTLEWOOD.

Salk Vaccine

SIR,—The Salk anti-poliomyelitis vaccine is prepared from monkey tissue cultures. Is it certain that injection of this preparation will not produce rhesus antibodies when injected into susceptible human subjects, most especially those already sensitized?—I am, etc.,

London, S.W.1. J. G. HUMBLE.

The Aftermath of Hysterectomy

SIR,—The letter of Dr. Winifred Coppard (*Journal*, April 2, p. 852) raises two separate issues. She suggests that gynaecologists may advise the performance of hysterectomy without ascertaining that their patients appreciate what that operation involves. This failure to inform the patient is always reprehensible, although it may sometimes be difficult to give an elementary lecture in the anatomy of the genital tract to a patient whose mind is hopelessly disorientated by hearing the word "operation."

The second implication is that patients may not be warned in advance of the changes (anatomical, hormonal, psychic, and domestic) that may follow in the wake of that operation. The reason that this warning is not given lies surely in the extreme variation of individual response and the difficulty in assessing how far that response is functional or organic. It is common experience that symptoms of the climacteric will rapidly occur in many women from whom both ovaries have been removed, yet in some cases there will be no such symptoms and a vaginal smear will show evidence of oestrogen activity. Conversely, failure of ovarian function may be established within three years in a significant percentage of women in whom one or both ovaries have been retained. The age of the patient and the operative technique may both be important.

The follow-up of these cases is not an easy matter, for the personality of the investigator may easily cause symptoms to be suppressed or exaggerated. The attitude of the surgeon before operation and during convalescence is also of great importance, and the conservative operator who rarely removes an ovary will get wonderful results from the assurance that "the womb is of no value, but of course the ovaries which make you womanly will be saved." It must be admitted that the radiotherapist can do an equally good line with his remark, "Just a small dose of rays to damp things down, and of course nothing need be removed." It is, however, my personal opinion that, with careful preoperative reassurance, early return to normal domestic life, including intercourse, and an operation that preserves the maximum ovarian function, any unpleasant aftermath is extremely rare; when it does occur it will usually be in a patient whose operation has been occasioned by a psychosomatic disorder.—I am, etc.,

Birmingham W. G. MILLS.

SIR,—Although one agrees with Mr. V. B. Green-Armytage's contention (*Journal*, April 16, p. 971) that disastrous results may follow the total ablation of both ovaries when performing a hysterectomy for non-malignant disease of the uterus such as fibroids, one cannot agree with his suggestion that the same results may follow treatment by irradiation.

In reviewing my own 990 cases[1] of metropathia haemorrhagica, fibrosis uteri, and fibromyomata of the uterus, I find that I performed myomectomy or hysterectomy in 502 cases and irradiation in 488—namely, deep *x*-ray therapy in 314 and radium treatment in 174. I reserved irradiation for all cases of metropathia, and *x*-ray therapy for metropathia and fibroid uteri not larger than a four-month pregnancy where the fibroid was interstitial and not undergoing degeneration, there was no other pelvic abnormality, and malignancy was not suspected.[2] Owing to the war I had to treat some cases of metropathia with radium for which otherwise I should have preferred *x*-ray therapy. The latter can now be done in one sitting lasting 64 minutes, and is, in my opinion, an ideal treatment for patients over the age of 40–45, for one can guarantee a permanent amenorrhoea and a reduction in the size of the uterus to one-third its original size, thus eliminating pressure symptoms. According to my follow up there is no loss of libido and no psychological disturbance.[3] In younger patients undergoing *x*-ray treatment the amenorrhoea lasts only about two years, and in two of my cases the patients later produced healthy babies.

In the case of radium treatment it is difficult to believe that the usual intrauterine dose could have any effect on the ovaries, considering their distance from the radium and the thickness of the uterine wall. I certainly have not encountered disastrous results following irradiation, such as have recently been described in your columns following the total ablation of both ovaries, and the consequent break-up of hitherto happy marriages.—I am, etc.,

London, N.W.8. L. MARTINDALE.

REFERENCES

1 Martindale, L., *Proc. roy. Soc. Med.*, 1948, **42**, 319.
2 —— ibid., 1938, **31**, 1010.
3 *J. Obstet. Gynaec. Brit. Emp.*, 1937, **44**, 109.

Chlorpromazine for Mental Hospital Patients

SIR,—It is always gratifying to hear of psychiatrists in mental hospitals taking an interest in those of their patients who have been ill for a long time. One cannot conceive any treatment, provided it does not produce irreversible structural damage, failing to be of benefit to these patients, because it would mean that during the period of treatment they will receive the observation and interest of the psychiatrist and his nurses, which they otherwise generally fail to receive. One has little doubt that chlorpromazine has indeed some effect in psychiatric illness, but one cannot believe that anyone will be favourably impressed by the accounts of it given in the *Journal* of April 9 by Dr. J. Lomas (p. 879) and Dr. C. P. Seager (p. 882). These two articles reveal what would be a quite astonishing state of affairs were it not so widespread. Those of your readers who are not psychiatrists should realize that the state of so-called improvement produced in the patients in these two hospitals which the authors allege was due to the drug was a state less good than that which can easily be produced by nothing more dramatic or expensive than a liberal regime.

One does not wish to say the drugs should not be tried out, but one cannot emphasize sufficiently that until psychiatrists are aware of the natural course of the diseases which they treat they should beware of attributing improvement to the drugs they are employing. Patients described in these articles have improved concurrently with the administration of chlorpromazine, but their final state is not as good as that found in many hospitals in this country who are without this drug.

The nursing problems which one of the authors describes are, one thinks, man-made, and if these patients were treated liberally then they would show an even greater improvement than that which he ascribes to the drug he employs.—I am, etc.,

Willerby, E. Yorks. J. A. R. BICKFORD.

Toxicity of Chlorpromazine

SIR,—I read with interest Dr. J. R. Tasker's paper on a case of fatal agranulocytosis (*Journal*, April 16, p. 950). Agranulocytosis is a complication of chlorpromazine that is not widely known, and, with the increasing use of this drug in general practice and other fields, it certainly must join the ranks of such drugs as thiouracil and phenylbutazone as a potential inhibitor of leucopoiesis, so that the possibility may be borne in mind (especially during the sixth week of treatment).

On referring to the manufacturer's booklet on chlorpromazine (first edition, undated like most of these booklets unfortunately are) I find that minor variations in the white cell count, either way, have been noted but "there has been no evidence of depression of leucopoiesis." The sex incidence of agranulocytosis attributable to chlorpromazine is interesting, although not altogether unexpected, as agranulocytosis from all causes is said to be two or three times more frequently encountered in females than in males.[1] Amidopyrine was at one time the outstanding toxic or sensitizing agent, and the inclusion of this drug (in the past) in pain-relieving tablets may, I suppose, partly account for the predominance of the disease in women. The mortality

rate is high, being in the region of 70% to 90%,[1] and it is therefore encouraging to know that three out of the four cases mentioned by Dr. Tasker recovered, in spite of their age (when leucopoiesis in any case is not at its best). Antibiotics were given to them all as prophylactic treatment; the three that recovered also received either cortisone, blood transfusion, or a combination of blood transfusion and folic acid (other lines of treatment suggested in the textbooks are: "pentnucleotide," leucocytic cream, and pyridoxine). As Dr. Tasker only mentions antibiotic treatment in his case, and as Dr. J. Lomas (*Journal*, August 7, 1954, p. 358) treated his patient purely on penicillin for ten days before resorting to cortisone, I wonder if there is any contra-indication to carrying out these "curative" methods, such as blood transfusion, immediately agranulocytosis is diagnosed?

It is wise to heed Dr. Tasker's warning that evidence of sensitivity to chlorpromazine, such as fever, jaundice, and skin eruptions during the early weeks of treatment, should be treated with respect, and should call for regular blood counts, especially in the light of the fatal case of jaundice reported by Dr. R. H. Boardman (*Journal*, September 4, 1954, p. 579), be this toxic or obstructive (see the letter by Drs. J. G. Macarthur and B. Isaacs, *Journal*, September 25, 1954, p. 754). In your leading article on September 4 (p. 581) you advise that if big doses are to be used a liver function test should be performed beforehand and the urine tested for bile while treatment goes on. Pallor of faeces must also be a warning sign. In a further leading article on chlorpromazine (*Journal*, February 5, p. 338) you conclude that as the effects of this drug are prolonged and for the most part irreversible, together with evidence of toxic action on the liver, great caution must be exercised in its use. In Dr. Tasker's article we have yet another reason for caution.

I doubt the advisability of using it for treating children suffering from intractable vomiting following whooping-cough (Dr. Howard Reeve, *Journal*, April 23, p. 1034), especially when ketosis and dehydration were probably accompanied by some impairment of liver function. With so many new drugs of considerable potency and toxicity available, it will be wise, especially for the general practitioner, to exercise great care and discrimination in using them, and, until we have better knowledge of their more remote effects, to confine their use to a carefully selected series in which constant supervision is possible.—I am, etc.,

Penygroes, N. Wales. JOHN H. OWEN.

REFERENCE

1 Wilkinson, J., in *British Encyclopaedia of Medical Practice*, vol. 1, p. 261. London.

SIR,—I was interested to read the account of chlorpromazine jaundice by Dr. A. G. W. Whitfield (*Journal*, March 26, p. 784). I have recently had a similar case.

A housewife aged 74 was admitted to hospital on February 16, 1954, with mental confusion and loss of memory. In October, 1954, she became restless and agitated. Chlorpromazine (200 mg. daily) was started on November 25, the dosage being increased to 300 mg. daily on December 2. Since admission she had vomited small quantities of food from time to time, but on December 6 copious vomiting began and the chlorpromazine was discontinued. On December 9 jaundice was first noticed. The jaundice steadily increased. It was accompanied by pale stools and bile in the urine. Her general condition deteriorated progressively and she died on January 25, 1955.

In brief, the post-mortem findings were as follows: external examination: thin, deeply jaundiced, with slight oedema of the ankles; respiratory system: lungs congested with oedematous lower lobes; cardiovascular system: normal, apart from a flabby myocardium and some old thickening of the mitral valve; abdomen: liver atrophic (880 g.) and firm, surface bile-stained with a fine nutmeg surface; gall-bladder shrunken; biliary tracts all free of obstruction; other viscera not significantly abnormal; central nervous system: C.S.F. jaundiced, brain rather atrophic with area of softening 2 cm. in diameter in the right temporal lobe.

Histologically, the liver showed severe centrilobular degeneration of the parenchymal cells with well-marked fatty change and deposition of bile. The appearance suggested a toxic change superimposed on mild chronic congestion. In sections of the myocardium there was some hypertrophy of the muscle fibres and a little interstitial fibrosis.

In common with other cases reported the clinical picture was one of obstructive jaundice, and the pattern of the liver function tests carried out supported this conclusion. The post-mortem findings suggested that the liver had already suffered mild damage as a result of anoxaemia due to heart failure. In life heart failure had not been apparent clinically, but her extremely restless condition made proper examination difficult. The total dosage of chlorpromazine (2.6 g.) was small, but the initial dosage (200 mg. daily) probably rather high. This is the first case of jaundice in over 100 cases treated with chlorpromazine by the present writer. Although a valuable drug in the treatment of certain psychiatric disorders, it should not be used unless definitely indicated and is probably dangerous in the presence of any liver damage already present.

I would like to thank Dr. J. O. P. Edgcumbe for the pathological reports.—I am, etc.,

Exeter. B. V. EARLE.

Cyst Formation Following Hernia Repair

SIR,—I was interested in the article by Mr. A. G. Rutter (*Journal*, April 16, p. 951) on the formation of a cyst following dermal implant repair of a hernia. Actually, in our experience at the Birmingham General Hospital this is more common than his article would suggest. We have now seen half a dozen of these, one of them five inches in length. Another contained large amounts of golden hair. Another complication we have observed is complete disappearance of the grafts. We have now completely abandoned the operation owing to these complications, and also to the fact that sepsis is not an infrequent occurrence. All these complications are, of course, not surprising in view of the completely unphysiological nature of the operation.—I am, etc.,

Birmingham, 4. G. T. WATTS.

Chicken-pox Quarantine

SIR,—Dr. Neil McDougall's letter (*Journal*, April 23, p. 1030) is interesting. In 1922 a patient aged 55 paid several visits to his brother, who had herpes zoster in a severe form. My patient developed herpes. His daughter, living with her parents and near full term in her third pregnancy, developed chicken-pox. Three days after the appearance of the rash she gave birth to a healthy boy, who developed the rash of chicken-pox at the age of 14 days. Mother and son did very well.

In the case of a mother suffering from small-pox at her confinement, the infant usually has the disease at the same stage as the mother.—I am, etc.,

London, S.W.12. S. G. ASKEY.

SIR,—I was surprised to read the suggestion in Dr. G. E. Breen's letter (*Journal*, April 23, p. 1030) that an attack of chicken-pox might be beneficial in protecting the patient from a subsequent attack of herpes ophthalmicus with concomitant iritis. Surely this view is contrary to observed fact. Thus, McNair Scott,[1] in a full discussion of the association of chicken-pox with herpes zoster, states that "it is very common for a person with herpes zoster to have a previous history of chicken-pox; about 70% of cases were found to have such a history in a recent survey of epidemic diseases in schools." In fact the author suggests the hypothesis that herpes zoster is a response of an immune person to an overwhelming dose of varicella-zoster virus. Likewise, Ker[2] states that "it is undoubtedly the fact that many adult patients suffering from herpes zoster are able to give a definite history of chicken-pox in childhood." It would seem more germane to the argument concerning the quarantine of chicken-pox to point out that exposure to chicken-pox can in an adult result in herpes ophthalmicus with risk of damage to the eye.

I would support Dr. Breen's statement that severe complications of chicken-pox do, exceptionally, occur. Besides

encephalitis, I have also seen as complications staphylococcal septicaemia, a gangrenous lesion of the anterior abdominal wall giving rise to peritonitis, and a few severe cases of pneumonia. I also know of a colleague who had a case in which perforation of the oesophagus occurred with fatal results. Even uncomplicated chicken-pox in the adult is generally quite an unpleasant experience, and in the female there is the risk of a residual facial scar being regarded as a disfigurement. I feel, therefore, that the doctor advocating indiscriminate and avoidable exposure to chicken-pox might ultimately find himself in difficulties.—I am, etc.,

Croydon. J. J. LINEHAN.

REFERENCES

1 Scott, McNair, in *Modern Practice in Infectious Fevers*, 1951, edited by H. Stanley Banks, p. 584. London.
2 *Ker's Infectious Diseases*, revised by C. Rundle, 1929, p. 222. London.

Corrosive Poisoning

SIR,—The article on corrosive poisoning (*Journal*, April 16, p. 962) cannot pass without comment. Under "Chemical Burns of the Skin," it is said: "These are usually due to strong acid or alkali spilled or splashed at work. They are seldom severe, as the substance is easily washed off." My criticism is directed only to the statement so far as it relates to sodium hydrate, commonly known as caustic soda, of which I have had many years' experience, and I have to say that burns from this cause may be very severe and that the substance is not easily washed off.

In 1930 at the alkali works with which I became connected there were 26 men off work with caustic burns. The treatment in vogue was copious washing with water and then application of bicarbonate of soda. The result was a burn which looked like an inlay of black leather in the skin; this took several weeks to heal, the gangrenous skin having to separate, leaving a granulating area, slow to heal. There is a latent period of 20 to 30 seconds after the contact of the caustic with the skin. If within this time a stream of 5% solution of ammonium chloride is directed on to the affected skin, no burn will take place; so that wherever there is a caustic soda risk that solution ought to be at hand for instant use. Caustic burns of the skin are almost unknown at the present day at these works, although the exposure is greater than it was then.

In the case of splashes in the eye the results are very serious with inadequate treatment: symblepharon, ectropion, intropion, corneal ulcer, corneal opacity, even loss of vision. All these have been abolished. I dare not trespass any further on your tolerance. The way that these eye risks were abolished was described in the *Journal* of June 19, 1943.—I am, etc.,

Bunbury, Cheshire. HERBERT TERRY.

REFERENCE

1 Terry, H., *British Medical Journal*, 1943, **1**, 756.

Agricultural Pesticides

SIR,—I was surprised to see aldrin and dieldrin in Dr. E. F. Edson's paper (*Journal*, April 2, p. 841) under the "Comparatively Safe" heading. These compounds were introduced to Britain some four or five years ago, and Messrs. Shell Chemicals Ltd. issued special instructions to insecticide manufacturers regarding the handling of aldrin and dieldrin in the production of typical insecticide mixtures—sprays, powders, and the like. The oral toxicity of dieldrin was quoted as eight times that of D.D.T. However, it appears that aldrin and dieldrin can be absorbed through the skin to a much greater extent than D.D.T., and that it is dangerous to walk across a floor carrying the dust of these chemicals, as the shoe soles would become contaminated and ultimately lead to absorption into the feet. Masks and special washable clothing—including rubber footwear—would have to be worn by workers.

While recognizing that preparations containing these compounds in dilute form may not be nearly as dangerous as the pure substances, considerable risk appears to attach to aldrin and dieldrin. The control of insects resistant to D.D.T. has led to the introduction of chemicals more and more toxic to human beings, the deadliest being the organic phosphorus compounds. Aldrin and its companion are not comparable with the latter, but are nerve poisons and could probably lead to chronic poisoning from contaminated clothing unless the worker at least uses rubber gloves, apron, and boots, and washes these thoroughly after use.—I am, etc.,

Walton-on-Thames. A. F. MCK. JACKSON.

Nocturnal Enuresis

SIR,—I have for some time past treated all cases of non-organic nocturnal enuresis by suggestive therapy to the child and varying doses of amphetamine. I have insisted on the children drinking not only their usual drinks but greatly increased quantities irrespective of the nearness to bedtime. Explanation is given to the child and the parents that the enuresis is a failure on the part of the bladder of remembering how much fluid it can take during the day when volition is brought into play. By its ability to hold urine for longer periods and by increasing amounts during the day does the child relearn control by night. The amphetamine in the first few nights of treatment keeps the child from sleeping and sends the child on many "excursions," increasing the child's confidence that at last it can be trusted at night.

I am unable to claim 100% cures as do the advocates of conditioning, but find the results excellent and certainly better than when the fluid intake is restricted. The child is more co-operative and helpful, feeling "grown up" because he is trusted and treated normally. I put forward this letter not to establish any new theory or more modern concept of treatment of enuresis but to remove ancient prejudices and injunctions not only from medical practice but from medical textbooks.—I am, etc.,

Sidcup, Kent. L. A. NICHOLS.

E.C.T. in Pregnancy

SIR,—With reference to the annotation on E.C.T. in pregnancy (*Journal*, April 16, p. 958) we would like to confirm the safety of this procedure.

During the last seven years we have successfully administered E.C.T. in 10 cases of pregnancy with no ill effects. The pregnancies have been between 3 and 8½ months' gestation. We do, however, deprecate the use of anaesthetics and muscle relaxants in these cases, as they involve an additional complication and risk. They are unnecessary when the new ectonus technique of E.C.T. is used, in which there is no sudden muscle contraction, and the clonic movements are eliminated. With the ectonus technique we do not consider any stage of pregnancy a contraindication to E.C.T.—We are, etc.,

R. J. RUSSELL.
Arlesey, Beds. L. G. M. PAGE.

Speaking Up

SIR,—Your correspondents blamed only the speakers at meetings for lack of intelligibility. The acoustic properties of lecture-rooms, often quite atrocious, should be also taken into account. Many amplification systems, installed to improve acoustics, are ineffective, or make things worse by increasing the effects of reverberation. The microphone provided for the speaker is usually strongly directional, and as soon as the lecturer turns his head a little (for instance, when trying to point out certain things on the blackboard or screen) amplification ceases, and intelligibility is reduced to the minimum. Also one must consider that a large proportion of the audience at medical meetings consists of elderly gentlemen, and a good number of them already suffer from more or less impaired hearing for high frequencies. Consequently their discrimination of speech in unfavourable circumstances is reduced. This is made worse when the lecture is read, because the audience is then deprived of a valuable aid to intelligibility—that is,

lip-reading. One should not deliver a lecture in a darkened room, and the lecturer should be positioned in a favourable light and favourable position from the point of view of the audience, so that listeners should be able to lip-read as much as possible.

Undoubtedly many speakers could improve their technique. Some would benefit from a little rehearsal with the aid of a tape recorder. Many would get such a shock from hearing a record of their own speech that they would change their mind and decide not to deliver the lecture. This is of course not necessary. A little practice could make a great difference. For instance, the lecturer could practise keeping his voice as low as possible. The higher the pitch of the voice the smaller the degree of intelligibility. Excitement, which is difficult to suppress, causes tension of the vocal cords and this raises the pitch of the voice. Practice can lessen this unpleasant effect.

Speakers who have doubts about their voice and intelligibility of their speech should not hesitate to take professional advice. For instance, speech therapists, employed in so many hospitals, could be very helpful, and it should not be below the dignity of the lecturer to ask for such advice. Perhaps some experts could produce a little booklet for medical speakers on the technique of delivering a scientific lecture.—I am, etc.,

London, W.C.1. L. FISCH.

An Occupational Hazard

SIR,—During the past year in casualty I have come across the following similar cases—which might be described as an occupational hazard. Each was a healthy young man in the butchery trade, presenting with a ¼–1 in. (6.4 mm.–2.5 cm.) long stab wound of right groin over the femoral canal, and the wounds lying in a transverse direction. All the patients were right-handed, and each stated they were boning frozen meat when the knife accidentally slipped through a part of the meat which had thawed out. The first case was in a 29-year-old butcher, who was brought in moribund although still just conscious. He had a 1 in. (2.5 cm.) stab wound over the right femoral canal. It was not bleeding when I saw him, but he had obviously lost pints of blood. An intravenous drip was put up immediately, but after 10 minutes, when only ½ pint (0.2 l.) of blood had gone into the patient, he began to bleed from the wound again, and collapsed and died in one minute. A post-mortem examination was not carried out, but I feel that as the wound measured exactly the same as the widest part of the 4-in. (10.2-cm.) long knife—that is, 1 in. (2.5 cm.) at the hilt—the knife probably penetrated the abdominal aorta. The other three cases were more fortunate in that the femoral vein was cut on one occasion, and only the skin and superficial tissue in the remaining two. All three were sutured after the bleeding vessels had been ligated, and made an uneventful recovery.

A master butcher present at the inquest on the first case stated that this was not the first fatal case he had come across. Still no protective clothing or shield fixed to the near edge of the table is yet adopted in this dangerous occupation.—I am, etc.,

Nottingham. EDITH FAULKNER.

Swallowed Hair-grips

SIR,—During recent weeks several articles and letters have been written concerning the fate of swallowed "kirbigrips." Opinions appear to be divided as to the treatment, particularly in small children. In the last week we have had to deal with such a case. The method used differed from those already described in the recent *British Medical Journals*, and is therefore being reported.

A small girl, aged 12 months, was admitted to the ward having swallowed a kirbigrip five hours previously. *X*-rays taken on admission and during the following week showed that it had not passed from the stomach. The child remained quite well. On the seventh day a James's magnetic tube (similar to a Ryle tube with a magnet being substituted for the usual metal tip) was passed through the mouth into an empty stomach. Under x-ray screening the grip was seen to become attached to the magnet. After several attempts it was manœuvred through the cardia and drawn into the oesophagus. Then the child was held upside down, and after gentle traction the kirbigrip was felt in the laryngopharynx and removed digitally. No anaesthetic was given. The whole procedure lasted 30 minutes. The child recovered rapidly, and was discharged after 24 hours' observation. She suffered no ill effects.

This is a simple way of removing a potentially dangerous object from the stomach without adding the hazards of surgical intervention. Perhaps we were lucky. It would be of interest to know if others have tried this method and have any improvements to suggest.—I am, etc.,

Old Windsor. MARGARET S. I. WILLIAMS.

Psychosomatic Appendicitis?

SIR,—I have read the annotation on "Psychosomatic Appendicitis?" (*Journal*, April 16, p. 960) with great interest. The suggestion was made that "perhaps the answer will be found when surgeons take psychosomatic histories from all their patients." I do not think this is a very practical suggestion—everyone knows that surgeons' notes on patients are necessarily brief, by reason of the comparatively large number of patients they see in a very short period.

I would be interested to know whether the writer of this annotation excludes so-called obstructive or recurrent appendicular colic. Superadded muscular spasm induced by overaction of the sympathetic would account for these recurrent attacks of pain far more than in the case of acute appendicitis, which is a pathological phenomenon. The fact that countless appendices which have been removed show no pathological lesion seems to me to support the psychosomatic theory.

It might interest readers to know I have had recurrent attacks of mild appendicular colic, which only occurs when I am driving a car and when I am under certain tension. For example, while driving to Edinburgh to sit an examination, I was seized with sharp stabbing pain localized to the right iliac fossa, which disappeared as rapidly as it came when I reached my destination. Whenever these attacks occur, I anxiously wonder if it will be necessary for me to have an operation.

One wonders if the condition is allied to "spastic colon." Perhaps a drug such as chlorpromazine would be indicated.—I am, etc.,

Halifax. J. W. WESTON.

"Half-minute" Thermometers

SIR,—I recently purchased a "half-minute" clinical thermometer of reputable manufacture which takes a full five minutes to register. Would it not be possible for thermometers to have issued with them not only a certificate of accuracy but also a certificate of time?—I am, etc.,

London, W.1. PETER GILBERT.

Anonymous Anaesthetists

SIR,—At the end of his most interesting account of "Recovery after Penetrating Wound of the Heart" (*Journal*, April 16, p. 952), Dr. R. W. Lawrie thanks "Mr. P. W. Bleasedale for permission to publish this case; also the anaesthetist, without whom the operation would have been impossible." Dr. Lawrie's tribute is just, because it is largely due to the advances in anaesthesia and the co-operation of the anaesthetists that a modern surgical procedure such as he describes can now be carried out. Anaesthetists are modest men, and not so much in the limelight as surgeons; but credit should be given where credit is due. Could Dr. Lawrie take off therefore the mask of anonymity and let us have the name of his anaesthetist, so that we can congratulate him, as well as his colleagues, on their brilliant success?—I am, etc.,

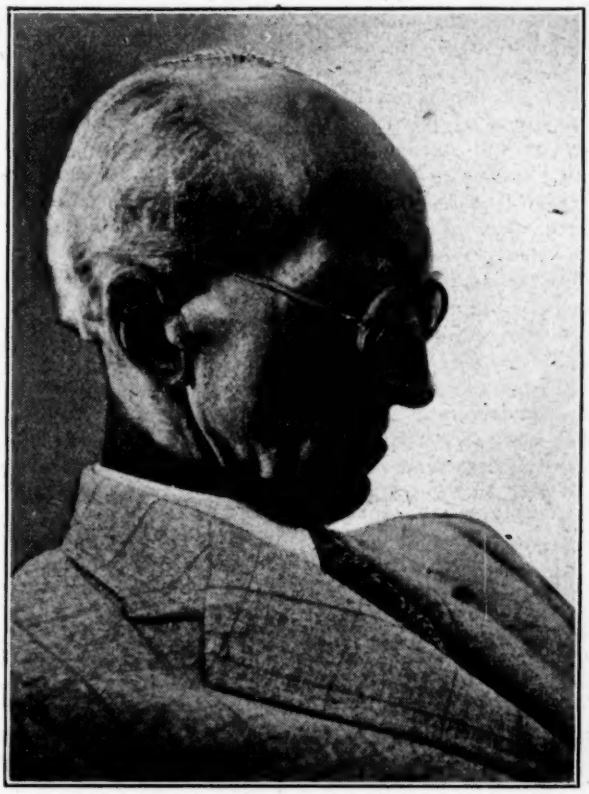
Edinburgh. JAMES A. ROSS.

Obituary

EGBERT MORLAND, M.D., F.R.C.P., F.R.C.S.

Dr. E. G. Morland, formerly Editor of the *Lancet*, died on April 26 in a nursing-home at York, aged 80 years.

Egbert Coleby Morland, fifth son of the fourteen children of Charles Coleby Morland, J.P., was born on September 3, 1874, at Croydon, and was educated first at the Whitgift School there and later at the Friends' School at Bootham, York. As a schoolboy he was something of an infant prodigy, showing an equal facility for languages and science. It was said that at the age of 14, his brother Harold, a recent senior wrangler, was the only member of the staff capable of teaching him mathematics; be that as it may, he left school with the Gilchrist Scholarship in the London matriculation examination too young to start the study of medicine. Proceeding to Owens College, Manchester, he took the London B.Sc. in biology, with first-class honours, in 1893. Still only 19 years of age, he started on his medical career at St. Bartholomew's Hospital, to which he won an entrance scholarship. He qualified in 1897 and graduated M.B. in the following year, winning the gold medal in physiology. Then followed a series of house appointments and a tendency to specialize in diseases of the eye, but his ambitions were frustrated by a severe haemoptysis and a long period of treatment in Switzerland. The severity of the catastrophe was mitigated by the loyalty of his fiancée, Mary Latchmore, who insisted on marrying the patient (in 1903) and devotedly nursed him back to health.



Egbert Morland's constitution was too frail and his tuberculosis too severe for him to return to specialist training and practice in London. He therefore decided to remain in Switzerland and to specialize in tuberculosis. That decision involved going back to school at Schiers College in the valley below Davos to pass the Swiss matriculation examination. A period of medical study at Berne under Kocher and Sahli ended with the acquisition in 1907 of the M.D., and, more important, the Federal Diploma, which gave him the right to practise in Switzerland. It was at about this time that Egbert Morland, with his architect brother, Geoffrey, entered the competition for the design and equipment of the King Edward VII Sanatorium for Consumption at Midhurst. Their essay was awarded the second prize, and some of their suggested features were incorporated in the final plan.

At that time the climatic treatment of tuberculosis was at its zenith and Davos was its Mecca, but in that centre competition from English and Swiss colleagues was sufficiently severe to make the prospects of a newcomer uncertain and arduous. After much consideration Egbert Morland decided to settle at Arosa, then a comparatively small resort separated from the railhead at Chur by a six-hour coach or sleigh drive. The choice was a good one, as the high altitude (6,000 feet) and its sheltered, sunny position soon made Arosa one of the leading centres in the Alps. A small sanatorium, the Villa Gentiana, was acquired, and the number of patients living in hotels and pensions grew so rapidly that Morland was soon overworked during the winter season. In an Alpine resort summers are always slack, and so he found time to write several original articles, and, in conjunction with the late Dr. Clive Riviere, an excellent little book on *Tuberculin Treatment*, which was so clearly written and so moderate in its claims that it remained the most reliable textbook on the subject for as long as tuberculin continued to be used as a therapeutic agent. Artificial pneumothorax was only just becoming established at that time, and Morland, although he never used it extensively, was one of the first British doctors to practise that form of treatment.

Morland took no part in winter sports and had no interest in mountain climbing; but he was a great walker, and his extensive knowledge of Alpine flowers, animals, people, and history made him a delightful companion. During the summer months he would take his turn to deputize for Swiss colleagues who looked after the population of the surrounding villages, some of which were very isolated and could be reached on foot only after five or six hours' walking. The villagers were too considerate to send so far for a doctor for normal events such as birth and death, and it was only the mysterious illness that called for a doctor's visit. Morland always considered his most profitable consultation to have been one involving ten hours' walking, a history taken from a small boy in a dialect which taxed Morland's linguistic powers to the utmost, a diagnosis (subsequently confirmed by the patient) of unripe apples, and a fee of two francs.

In 1914 the railway, which had taken several years to build, was completed, but by the time the first train had arrived war had broken out and the flow of British patients had stopped abruptly. By 1915 there was virtually no practice left, and Morland had no option but to return to England to try to make a living by private consulting practice, helped by the writing of occasional articles for the medical press. The latter

activity brought him into contact with Dr. (later Sir) Squire Sprigge, who liked his literary style, and it was not long before he received an invitation to become assistant editor of the *Lancet*, a post he held from 1915 until he succeeded Sir Squire Sprigge as editor in 1937 at the age of 63. Morland soon made his mark as a medical journalist; by vigorous pruning of all unnecessary words and by careful polishing he achieved a lucid, apparently effortless style in which no word was wasted. The somewhat austere effect of his prose contrasted with the frequently Puckish, almost Chestertonian, context of many of his leading articles. His private correspondence was almost confined to the postcard, a scanty plot on which he contrived to cultivate both substance and wit.

In 1936 Morland was elected a Fellow of the Royal College of Surgeons, and in 1941 a Fellow of the Royal College of Physicians. The field of medicine now covered by the term social medicine always interested him, particularly the problems of old age, and he served as vice-president of the Section of Medical Sociology at the Annual Meeting of the B.M.A. at Plymouth in 1938. He retired from the editorial chair of the *Lancet* in 1944 and went to live near his married daughter and her young family in the Yorkshire Pennines, where he combined free-lance journalism with gardening. His later years were saddened by the loss of his wife, who died suddenly in 1948, and shortly afterwards by blindness, which became almost complete, and by a fractured femur. He remained mentally alert, however, and derived much consolation from the wireless, especially from the Third Programme.

Egbert Morland was born a Friend, and was throughout his life an active member of the Society. He was one of the founders of the Quaker Medical Society, which came into being shortly after the war of 1914–18. Unlike many Quakers, he was fond of music and the visual arts, and it was characteristic of him in his later years that he made a weekly practice of brightening the austere seventeenth-century Meeting House at Wooldale with flowers from his garden.

We are indebted to our colleagues on the staff of the *Lancet* for the following composite pen picture of their former chief:

One week in February, 1915, when the *Lancet* was going to press, its editor, Squire Sprigge, stopped the printing machines so that he could include a summary of a German pamphlet describing the food resources of the German nation. This uninvited article, which had come unexpectedly from Switzerland, was Egbert Morland's introduction to the *Lancet* editorial circle. At once intrusive and appropriate, it was not uncharacteristic. Lucid, accurate, and highly topical, it arrived at an awkward moment and yet was too important to be ignored. For the first time the *Lancet* was exposed to Morland's sense for exciting news or significant principles hidden behind an apparently dull collection of facts and figures, printed perhaps in small type in a foreign language. Later in 1915, on his way through London after a tour of duty with a Friends' relief unit on the Marne, he dropped in at the *Lancet* offices on the corner of the Strand and Bedford Street. Dr. Sprigge, who was short-handed, suggested that he should "stay and help." What began as a casual afternoon call endured as an association of over 30 years.

Morland's career had been twice checked—once by illness and again by war—but in the *Lancet* office he found congenial scope for his talents. His experience as a clinician, his interest in tuberculosis, his concern for the new science of social medicine, his facility for languages, and his knowledge of Europe were all assets to the journal. His lack of journalistic experience mattered less than might have been expected, for it was his set technique to tackle even the familiar by unfamiliar methods. He had not been long at the *Lancet* before problems of printing, make-up, and editorial administration had captured his interest and engaged his ingenuity. For the arrangement and selection of illustrations he had both skill and taste, and even as editor he occasionally indulged his enjoyment of his craftsman's aptitude. The *Lancet* traditions held in bounds the overzealousness and exaggeration which were the reverse of his brilliance and driving power. If Morland got things done, Sprigge was able to restrain him from overdoing things. And if this restraint sometimes irked Morland, who had after all started a new career in middle age, he soon found in the editorship of *Maternity and Child Welfare*, to which he was appointed in 1917, an opportunity to try his independent wings.

As the years between the two wars passed, the staff and scope of the *Lancet* broadened. But when, in 1937, Dr. Morland succeeded Sir Squire Sprigge, a dubious peace was already giving way to an uncertain war, and he had had little time to settle in the editorial chair before the *Lancet* was evacuated to Aylesbury in 1939.

For the next five years he edited the journal from what he called his "pocket office" in an old-fashioned dwelling-house in Temple Street, and lived "above the shop." If he regretted the limitations imposed on his work by war he never said so. Instead of repining for the opportunities and contacts of London, he joined with zest in the busy life of a market town. He quickly made friends with the local hospitals and doctors; he attended the meetings of local societies; and he took a benevolent interest in civic problems. Being Morland, he could not live a country life without dressing for the part; and his highly individual version of the formal clothes of an editor-about-town now gave way to rough tweeds, a beret, and, latterly, even a beard.

As the war went on it became clear that, though Aylesbury itself was nowhere in particular, it was on the way to several other places; and people began to drop in at the *Lancet* office. It might be an Oxford don, a Cambridge professor, a general in battle-dress, an admiral in gold braid, an American colonel, or a Quaker neighbour with a basket of apples from a Buckinghamshire orchard. Morland offered them all the same sincere if astringent welcome, and they all found his conversation stimulating if sometimes puzzling; for his passion for lucidity was sporadic and always stopped short at print. To the reader he was usually considerate; but his correspondents and callers had to fend for themselves. On a postcard—in his view the ideal vehicle for correspondence—he was oracular, and in conversation cryptic. But what he said, and didn't say, was usually worth pondering. As one of his staff once pointed out:

> "He seldom asked a question directly or answered one comprehensibly, but by a series of hints, sniffs, and silences spurred others into spirited performances, which he managed by only the lightest of guiding reins. He was not only a good journalist, but a cause of journalism in others."

E. C.-J., who so largely shared the anxieties and difficulties of the war years with him, also found him a congenial chief.

> "Egbert Morland was nearly the ideal editor for the newcomer to journalism. He could assess in an instant the shadowy ideas that keep floating up when one lacks confidence and experience, and if one of them seemed potentially valuable he would imperceptibly add the deft touches it needed and guide one's hand so tactfully that one forgot how much of the finished article was a result of his skill.
>
> "His conversation was unique. Strangers often found it incomprehensible, for he assumed that his hearers' lines

of thought must run parallel with his own. After five minutes' silence he would break in with a terse comment that seemed wholly irrelevant except to his intimates who had learnt the technique—to link it not with the last remark made but with Egbert's own last contribution to the conversation, which had been exercising his astute mind ever since.

"On tuberculosis and child welfare he was an authority—and on these subjects he could write and speak with brilliant originality. In other branches of medicine he may have seemed to take disproportionately little interest; yet when brought a newly written paper to judge nobody would grasp its significance more quickly and accurately, and few could spot snags and fallacies in its conclusions so surely and certainly."

In the later years of the war Morland's disabilities forced him to leave an increasing amount of routine to his staff; and when at the end of 1944 the editorial office was moved back to London he felt free to remain behind in active retirement.

D. T. BARRY, M.D., D.Sc., F.R.C.S.

The death occurred in London on April 15, after a short illness, of Professor D. T. Barry, for 35 years professor of physiology at Queen's (now University) College, Cork. He was 84 years of age.

David Thomas Barry was born at Ballyannahan, Co. Cork, in 1870. He received his medical education at Queen's College, Cork, and graduated M.B., B.Ch. at the old Royal University of Ireland in 1894. He then spent some years in general practice in England, and took the D.P.H. of Liverpool University in 1904, having proceeded to the M.D. in the previous year. It was about this time that he decided to return to the study of physiology, and he spent some years in London, working with Starling, and at the Universities of Berlin and Heidelberg.

Barry obtained the Fellowship of the Royal College of Surgeons of England in 1907, and in the same year was appointed to the newly created chair of physiology at Queen's College, Cork, a position he was to fill until 1942, when he retired as emeritus professor. One of the first tasks in his new appointment was to create a separate department of physiology, which, up to 1907, had been linked with anatomy, and within a few years he had the satisfaction of seeing a physiological laboratory established and in use. Later a histological laboratory was added, and this was soon followed by the provision of similar accommodation for biochemistry and experimental physiology. When he retired Barry estimated that during the 35 years he was professor at Cork over 2,000 students had passed through his hands. In him they had a teacher who was also an enthusiastic investigator: his inspiration turned the thoughts and endeavours of many of his pupils to original research. As one of his colleagues wrote of him some years ago: "To hear him talk about the central nervous system, to watch him draw cross-sections of the brain and cord at various levels, to see him doing heart–lung perfusions, demonstrating the electrocardiograph, and illustrating the action of curare—in 1917—was to be given a preview of the influence of applied physiology on the clinical practice of the 1930's and 1940's. Barry was a forthright teacher, as all great teachers are. Someone said of him that he spoke English quite as well as he did French; the remark was meant to imply Barry's many contacts with the French school of physiology."

Barry was deeply influenced by the teachings of Claude Bernard, and after the first world war paid frequent visits to France and carried out research with Gley at the Collège de France in Paris, at the Sorbonne, with A. and B. Chauchard, and with the Lapicques at the Institut Marey and at the Laboratoires Maritimes de Dinard. He was appointed a Chevalier of the Legion of Honour in 1928 in recognition of this work.

His writings, numbering over 50 papers, appeared in the *Journal of Physiology* and other journals, and, while he covered a wide range of subjects in these communications, he wrote frequently on heart perfusion and electrocardiography. He also translated and condensed numerous papers for *Physiological Abstracts*. For many years he was an external examiner in physiology, in particular for the colleges of veterinary surgeons. In 1918 the National University of Ireland conferred on him the honorary degree of D.Sc.: he was a member of the Senate of the University from 1915 to 1919. He is survived by his widow, formerly Mlle. Marie Yvonne Boiret, whom he married in 1908, and two sons, Claude Thomas Barry, an anaesthetist, and Declan René Barry, a pathologist.

Dr. E. F. McCARTHY writes: The announcement of Professor Barry's death must have aroused vivid memories in the minds of the many Cork doctors who were privileged to be his students. A surgeon with the best qualifications, he was appointed to the chair of physiology in Cork in 1909 during the presidency of Sir Bertram Windle. He was a worker in Starling's laboratory before this, and his subsequent development was greatly influenced by his training in University College, London. His interests ranged widely in the field of physiology, as the titles of his papers in the British and French physiological literature show, but he was mainly concerned with the cardiovascular and respiratory systems. During his long tenure of the chair in Cork he published continuously. His family connexions with Paris induced him to spend his holidays there, where he worked with different French physiologists and where he was well known and very friendly with such scientists as Lapicque. French art and history attracted him strongly, and he was known to lecture and write very competently on such diverse subjects as the Valois monarchs and pointillism. His command of the French language was quite remarkable, and physiologists in general are familiar with his many excellent abstracts of French scientific literature. Professor Barry was a most conscientious and up-to-date teacher who was more conversant with current physiological literature than most physiologists. A strictly self-disciplined and hard worker, his example has a very salutary effect on his students, who greatly respected his detachment, fairness, and personal dignity and the fact that he treated them as grown-up individuals with a fully developed sense of responsibility. His apparent aloofness frequently hid a deep concern for their welfare and a respect and liking for their qualities, of which they can have had little awareness.

D. W. HOODLESS, O.B.E., B.Sc., L.M.S.S.A.

We record with regret the death on April 15 of Dr. D. W. Hoodless, who for over forty years was a much-loved figure in Fiji, where he rendered invaluable service first as a teacher and later as principal of the Central Medical School at Suva. He and Mrs. Hoodless were on holiday in England when he was taken ill and admitted to Addenbrooke's Hospital, Cambridge, where he died at the age of 67.

David Winn Hoodless was born at Walkeringham, Nottinghamshire, on May 16, 1887, and was educated at Sheffield and at King's College, London, graduating

B.Sc. with honours at London University in 1910. He went to Fiji in 1912 as headmaster of the first provincial school for native boys, and later he was appointed headmaster of Queen Victoria School. From 1919 to 1921 he studied medicine at Charing Cross Hospital, but went back to Fiji to become, first, inspector of schools, and then director of education. Resuming his medical studies in England in 1928, while on two years' leave, he again returned to Fiji to become the first principal of the Central Medical School for South Pacific natives, which was opened in 1930. Five years later, when he was well into middle age, he qualified in medicine by taking the diploma of L.M.S.S.A., illness having prevented him from taking the final examinations in 1929. Since 1953 he had been *The Times* correspondent in Fiji.

As principal of the medical school Hoodless helped hundreds of natives of the South-west Pacific territories administered by five Colonial powers to embark on careers useful to their home communities, where they provided a medical service which would have been beyond the means of their respective governments if all posts had been filled by European practitioners. His work in Fiji was always in great part with the Fijian, for whom he had a real affection. He was honorary secretary of the Fiji Branch of the British Medical Association from 1937 to 1940 and president of the Branch from 1941 to 1943. Retiring from the post of principal in January, 1947, he was appointed O.B.E. in the Birthday Honours of that year. He was also an Associate of King's College, London. He leaves a widow, formerly Miss Hilda J. Adlington, of New Zealand, whom he married in 1923, and one daughter, to whom the deep sympathy of all his friends is extended.

A colleague writes: Throughout the island territories of the South-west Pacific, as in a much wider field, the name of Hoodless was well known as the principal of the Central Medical School in Suva, a post he had held for 16 years and from which he retired in 1947. By his death many hundreds of graduates from this well-known school have lost a real friend and a personal adviser. They, and the peoples of the South Pacific generally, owe him a very great debt because he was a teacher to whom family problems and the guidance of youth through the inevitable difficulties of adolescence were as real, or more so, than mere academic learning. The Central Medical School in Fiji draws its students from many groups of islands, and the personal friendship he extended to them all during the formative years of their lives, and while they were in surroundings strange to many of them, had a lasting effect on their character, and it is to his guidance and teaching that the high professional standard and traditions of the assistant-medical-practitioner system in the South Pacific is largely due. Apart from his professional work, Hoodless was a man with many human interests. He had an intimate knowledge of the Fijian language, and of Polynesian and Melanesian customs, and he had a multitude of friends among all races and all strata of society, by all of whom his passing will be deeply mourned.

Dr. J. C. PEARCE, who practised in Norfolk and was well known for his keen interest in local affairs as well as for his work for the B.M.A., died suddenly in a Norwich nursing-home on March 31, nine days after his 73rd birthday. John Cuthbert Pearce was the younger son of Canon R. J. Pearce, vicar of Bedlington, Northumberland, and honorary canon and rural dean of Newcastle. He was educated at Durham School, where he was King's Scholar, Durham University, and the College of Medicine, Newcastle-upon-Tyne, graduating M.B., B.S. in 1906. Two years later he proceeded to the M.D., being awarded the gold medal for his thesis. After graduation he held the appointments of assistant demonstrator of anatomy and physiology in the Durham College of Medicine, and assistant medical officer at St. Marylebone Infirmary. Subsequently he went into general practice as assistant to Mr. William Robinson at Sunderland, and was appointed honorary assistant physician to the Royal Infirmary and honorary assistant surgeon to the Sunderland and Durham County Eye Infirmary. In 1912 he entered into partnership with the late Dr. A. Ll. Vaughan, who died on the 28th of last month, at Diss, Norfolk, where he soon identified himself with the life of the community, and where he lived and worked for the next 43 years, except for his period of service in the first world war. Attaining the rank of captain in the R.A.M.C., he was first attached to the King's Own Yorkshire Light Infantry, and was wounded while serving in the line, and later worked in a Red Cross hospital, being awarded the Red Cross medal. After the war he became more and more absorbed in local affairs. Elected to the Norfolk County Council in 1922, he remained a member until 1930, and four years later he became chairman of the Diss Urban District Council, being also chairman of the governors of the local secondary school and of the county ambulance committee. He gave a good deal of his spare time, such as it was, to further the work of the British Medical Association. Chairman of the East Norfolk Division in 1946–7, he was a member of the old Insurance Acts Committee and its successor, the General Medical Services Committee, from 1943 to 1951, and of the Rural Practitioners Subcommittee over the same period. Another committee on which he served was the Central Medical War Committee, from 1944 to 1950. He was also a member of the Council of the B.M.A. for two sessions from 1948 to 1950. For some years he was a member of the local panel committee and, after the inception of the National Health Service, of the Norfolk Executive Council and the local medical committee. Until about a year ago he was a member of the Medical Practices Committee. Between 1920 and 1930 he was chairman of the Diss branch of the South Norfolk Unionist Association. A keen and active member of the Manchester Unity of Independent Oddfellows for about 30 years, he was a past provincial grand master of the Bury St. Edmunds district. He often deplored the fact that the ideals of the friendly societies were disappearing under the impact of organized charity and the welfare state. He was also a justice of the peace and deputy chairman of the Diss bench. A keen golfer, he was responsible for the revival of the Diss club after the first world war, and presented the club with its first cup when he was captain in 1925, winning the trophy himself three years later. Dr. Pearce believed in service to his fellow men and in the ideals of practical Christianity, which found further expression in his work for the British and Foreign Bible Society. He leaves a widow, formerly Miss Victoria Helen Bisset, whom he married in 1909, and one son, Dr. Ian C. B. Pearce.

Dr. J. A. PRIDHAM writes: The sudden death of Dr. J. C. Pearce has removed from the profession a fine example of the best type of general practitioner. He was a good doctor held in high regard and indeed affection by his patients, and greatly respected by his medical colleagues. Though he had a busy practice he found time for a multitude of activities of service to the community in which he lived, and to help the organized medical profession both locally and nationally. Those who had the privilege of his friendship knew him to have a fine sense of humour, and his conversation was illumined with wit. His courtesy and consideration were a part of the man. Perhaps his character can be summed up by saying that he was, in the best sense of the word, a gentleman. Last year, when he left the Medical Practices Committee, of which he had been a member since 1948, his colleagues gave him a farewell luncheon to show their appreciation of one whom they would always remember with esteem and affection. March 31 saw the end of a life of service.

Medical Notes in Parliament

BAN ON HEROIN

The manufacture and export of heroin will not be permitted after December 31, 1955, except for small quantities for purely scientific purposes. The Government's decision to this effect was announced in the House of Lords on April 28 by Lord MANCROFT, Under Secretary, Home Office. He said that, as adequate supplies had hitherto been manufactured in this country, imports had not been authorized for many years. It was intended to maintain the ban on importation.

The Government had taken the decision to give effect to a resolution adopted by the U.N. Economic and Social Council at its 18th session urging that all governments should prohibit the manufacture, export, and import of the drug, except for scientific purposes. The advice of the appropriate statutory advisory bodies had been taken.

Viscount ELIBANK said that Dr. Arthur Douthwaite, senior physician at Guy's Hospital, had stated in the *British Medical Journal* (April 9, p. 907) that the banning of this pain-killing drug was an astonishing move that would inflict much hardship on a multitude of patients. One of the best-known physicians in Edinburgh, Dr. A. B. Flett, had also written to him saying it was iniquitous that this most useful and often necessary drug should be banned. Lord MANCROFT said the Government was aware of these opinions. On the other hand, adequate supplies of a perfectly good substitute were now available. The purpose of the Government's action was to facilitate the world-wide banning of the traffic in this extremely dangerous drug. They had taken the opinion of the statutory bodies they were under obligation to consult—the Central Health Services Council, the standing medical advisory committee, and the appropriate bodies in Scotland and Northern Ireland. The Government could not do more than follow the technical advice and guidance given by them.

Viscount ELIBANK said it appeared from the information given to him that there was no satisfactory substitute for the drug. Lord HADEN-GUEST asked whether it was not a fact that the whole medical profession, so far as could be ascertained, was behind the order. Lord MANCROFT replied that that was the information available to him. The vast weight of evidence was in favour of the move.

Treatment at Broadmoor

Mr. T. DRIBERG (Maldon, Lab.) asked the Home Secretary if he was aware that a medical report by the Principal Medical Officer of Brixton Prison, dated February 14, 1953, stated that a prisoner (whose name has been given) was sane and fit to stand trial on a charge of attempting to murder his wife, and recommended him as suitable for voluntary treatment in a mental hospital; that, at his trial five days later, this man was found guilty but insane, and ordered to be detained during Her Majesty's pleasure, and that he was still detained at Broadmoor, where his wife and other relatives had found him in apparently normal health; and if, in these circumstances, he would allow an independent medical examination of this patient.

Major G. LLOYD-GEORGE, replying on April 28, stated that the responsibility for deciding when a Broadmoor patient was fit to be transferred or discharged rested on the Home Secretary; and his predecessors and he had consistently taken the view that the expert staff of psychiatrists at Broadmoor, who had the patient under constant observation, were in a better position than an outside doctor to advise the Home Secretary on the patient's mental state and future prospects. The answer was, therefore, "No."

Mr. DRIBERG said that Dr. Mathieson, of Brixton, had also said that the man was suffering simply from a mild anxiety neurosis, which should yield to psychiatric treatment, but since he had been in Broadmoor he had had no such treatment. It was obviously impossible for the efficient and conscientious staff at Broadmoor to give proper psychiatric treatment to the large number of patients with whom they had to deal. In these circumstances, would the Home Secretary consider getting an independent opinion or transferring the man to a mental hospital, where he could be treated? Major LLOYD-GEORGE said he was aware of the opinion Mr. Driberg had referred to, and he had gone into the case himself with great care. On the information he had he did not think anything could be done, but he was prepared to look at the matter again.

Tuberculosis in Malaya

Mr. H. HOPKINSON, Minister of State for Colonial Affairs, in a statement on April 26 about the incidence and treatment of tuberculosis in Malaya, said that no detailed survey on a sufficiently large and representative section of the population had been carried out, and an accurate guess was further hampered by the fact that many deaths were certified by non-medical persons, and no clear indication could be obtained from the figures given as death from tuberculosis. Local surveys on specially selected groups had disclosed an incidence of between 5 and 6 active cases of pulmonary tuberculosis per 1,000. It was considered that, if a survey were taken of all sections of the community, the figure would be somewhat higher. The new Lady Templer Tuberculosis Hospital was expected to be opened this year and would provide further beds for treatment of cases that were likely to improve. It would also provide an opportunity for research work into this disease in Malaya.

Food Hygiene Council Formed

The membership of the Food Hygiene Advisory Council has been completed, and was announced by the MINISTER OF AGRICULTURE, FISHERIES, AND FOOD on May 2. The chairman is Lord Strang, and the 17 members are:

Mr. S. W. Barnes, secretary to Board of Governors, King's College Hospital; Hon. Daphne Courthope, councillor, Battle Rural District Council; Mr. H. Crane, national industrial officer, National Union of General and Municipal Workers; Mrs. J. H. Engwell, Alderman of Barking Borough Council; Mr. C. W. Fulker, secretary, Parliamentary Committee, Co-operative Union Ltd.; Mr. J. Fuller, principal, Catering Department, Battersea Polytechnic; Mr. C. Leslie Gillitt, past president, National Federation of Grocers' and Provision Dealers' Associations; Dame Florence Hancock, member, General Council, T.U.C.; Mr. J. D. Hiscock, assistant general secretary, Union of Shop, Distributive and Allied Workers; Alderman F. J. Jackson, chairman, Clean Food Guild, Leicester; Miss A. Lumby, chairman, Food Hygiene Committee of Women's Group on Public Welfare; Mr. K. McCullum, director of Trust Houses, Ltd.; Sir Frank Shires, past president, Food Manufacturers' Federation; Sir Harry Sinderson, county director for Sussex of the St. John Ambulance Association; Mr. G. Squire, past president, National Federation of Meat Traders' Associations; Mrs. James Tweed, chairman, House Committee, St. James' Hospital, Balham; Mr. D. T. Williams, Alderman of Cardiff Borough Council.

The Salk Vaccine

Mr. ERIC FLETCHER (Islington, East, Lab.) asked the Minister of Health for a further statement about poliomyelitis vaccine in view of the decision taken in the United States to suspend all injections of Salk vaccine made by the Cutter Laboratories. Mr. IAIN MACLEOD stated on May 2 that he was aware of the Press reports of action by the American authorities. A small field trial was being carried out by the Medical Research Council. All vaccine used in this trial, whether imported or manufactured here, would first have been the subjec of rigorous tests by the M.R.C. Plans for large-scale immunization were dependent on the Minister of Health being satisfied, so far as was humanly possible as a result of these tests and trials, that the vaccine to be used was both efficient and free from danger.

Mr. FLETCHER asked whether any supplies of Salk vaccine from the Cutter Laboratories had been received in this country, and whether the Minister was satisfied that all

possible information from the United States would be received to enable the Ministry's experiments to be continued. Mr. MACLEOD said that no Cutter vaccine had been received in this country. The Ministry was in close touch with the American authorities on all aspects of the problem.

Mr. R. W. SORENSEN (Leyton, Lab.) asked whether the Minister had yet had information from America or elsewhere about the cause of the deleterious effect of what might be a very beneficial vaccine and whether, when he was assured that no further deleterious effect was likely to arise, progress would be made in distributing the vaccine. Mr. MACLEOD said he had no information so far beyond the Press reports. As soon as the Ministry was absolutely satisfied that the vaccines were safe as they could humanly be made there would be no delay in going ahead.

Lists of Patients for Voting

Mrs. B. CASTLE (Blackburn, East, Lab.) asked the Minister of Health whether he was aware that political party organizations were asking doctors for lists of patients for the purpose of the postal vote at the General Election; and if he would instruct N.H.S. doctors to refuse to give this information in respect of N.H.S. patients.

Miss PAT HORNSBY-SMITH stated that the Minister was certainly not aware of any such arrangements, and if Mrs. Castle would supply the Minister with the evidence she had he would investigate. The vote was secret, and in an individual capacity it was certainly helpful to see that as many people as possible voted.

Mr. HERBERT MORRISON (Lewisham, South, Lab.) asked for an assurance that neither directly nor indirectly would those associated with the Health Service co-operate with any political party association in the forthcoming General Election. There was the strongest impression in the last election that such malpractices did take place.

Miss HORNSBY-SMITH gave an assurance that the Health Service would not be used that way. Mr. MORRISON asked if, in view of the allegations, the Minister would make a statement later in the week. Mr. IAIN MACLEOD said he would look into it at once. Whether he made a statement depended on what he found.

Medico-Legal

DEATH FROM CHLORAMPHENICOL

A death from aplastic anaemia due to chloramphenicol was the subject of an inquest before Dr. H. N. Stafford, coroner, at Hammersmith on March 21. The patient, a 5-year-old girl, developed bronchitis in April, 1954, and her medical attendant, Dr. F. T. F. Lutter, prescribed "chloromycetin" in a dosage of "one teaspoonful three times a day." She was on this dosage for about three days, and the bronchitis cleared up very quickly. On November 24 the child was again brought to her doctor. She had a rash on her face and legs, not purpuric, and enlarged tonsils. The doctor thought it might be a toxic rash. He did not connect it with the administration of chloramphenicol. Later a blood count was taken, and on December 1 the child was admitted to the Victoria Hospital for Children, Tite Street, Chelsea, with a diagnosis of aplastic anaemia. Treatment by blood transfusion was without avail, and the patient died on March 3, 1955. Dr. F. E. Camps, consultant pathologist, conducted the post-mortem examination and confirmed the cause of death as aplastic anaemia. This condition, he said, was an extremely rare complication following the use of chloramphenicol, and he observed that the drug ought to be used with discretion. He did not think a doctor could forecast the condition, and blood counts were not practicable in every case. The coroner recorded a verdict of death from misadventure.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending April 16 (No. 15) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	7	2	3	0	3	14	1	3	1	0
Dysentery	1,191	87	328	9		919	121	273	4	3
Encephalitis, acute	6	1		0		2	0	0	0	
Enteric fever:										
Typhoid	2	0	1	0		1	1	0	0	0
Paratyphoid	2	0	1	0		5	0	0	0	0
Food-poisoning	156	17		0		88	9		6	
Infective enteritis or diarrhoea under 2 years				8	10				12	14
Measles*	32,969	3291	270	454	304	1,912	67	144	92	281
Meningococcal infection	28	3	18	1	1	24	1	18	1	2
Ophthalmia neonatorum	39	1	7	0		35	4	12	0	
Pneumonia†	804	45	282	13	6	451	17	185	10	0
Poliomyelitis, acute:										
Paralytic	14	1	1	0	2	10	0	3	0	3
Non-paralytic	6	0				7	1			
Puerperal fever§	253	25	9	0	1	185	24	14	0	
Scarlet fever	597	38	67	48	27	994	60	137	38	29
Tuberculosis:										
Respiratory	609	50	132	20		751	95	168	32	
Non-respiratory	67	3	28	1		111	9	20	2	
Whooping-cough	1,474	88	102	30	30	1,980	69	248	37	19

DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	1	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0	0		0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	0	3	0	0	7	0	0	2	3
Influenza	30	0	2	0	6	6	1	1	1	0
Measles		0	0	0	0		0	0	0	1
Meningococcal infection		1	1				0	2		
Pneumonia	315	46	30	14	10	189	26	22	8	4
Poliomyelitis, acute	2	1			0	0	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	87	11	9	4	5	90	10	10	0	6
Non-respiratory		0	2	0	0			1	0	3
Whooping-cough	1	1	0	0	0	2	0	0	0	1
Deaths 0–1 year	213	23	40	7	12	218	29	42	8	10
Deaths (excluding stillbirths)	5,913	864	616	125	210	5,092	703	577	129	178
LIVE BIRTHS	7,103	1065	1034	227	400	6,339	955	769	261	311
STILLBIRTHS	203	28	22			206	21	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

In England and Wales during the week ending April 16 the largest rises in the number of notifications of infectious diseases were 6,136 for measles, from 26,833 to 32,969, and 164 for whooping-cough, from 1,310 to 1,474, and the largest falls were 263 for dysentery, from 1,454 to 1,191, 68 for scarlet fever, from 665 to 597, and 68 for acute pneumonia, from 872 to 804.

The number of notifications of measles was the largest in any week since this disease was made notifiable. The largest increases during the week were 892 in Middlesex, from 1,705 to 2,597, 518 in Surrey, from 952 to 1,470, 480 in Essex, from 1,689 to 2,169, 423 in Southampton County, from 553 to 976, 404 in Kent, from 848 to 1,252, 366 in Warwickshire, from 3,199 to 3,565, 328 in Leicestershire, from 280 to 608, 275 in Lancashire, from 1,298 to 1,573, 263 in Buckinghamshire, from 389 to 652, 260 in Cheshire, from 574 to 834, 239 in Sussex, from 205 to 444, and 202 in London, from 3,089 to 3,291, and the largest exceptions to the general rise were decreases of 139 in Nottinghamshire, from 881 to 742, and 81 in Yorkshire West Riding, from 3,807 to 3,726. Only small variations occurred in the local trends of scarlet fever and whooping-cough. 7 cases of diphtheria were notified, being 2 more than in the preceding week.

20 cases of acute poliomyelitis were notified; these were 11 more for paralytic and 2 more for non-paralytic cases than in the preceding week. The largest returns were Lancashire 4, Yorkshire West Riding 3 (Leeds C.B. 2).

The largest centres of dysentery were Lancashire 451 (Oldham C.B. 81, Manchester C.B. 55, Blackburn C.B. 52, Blackpool C.B. 43, Liverpool C.B. 30, Royton U.D. 27, Chadderton U.D. 25, Whiston R.D. 18, Leyland U.D. 12, Stretford M.B. 11, Salford C.B. 10, Middleton M.B. 10), Durham 193 (Easington R.D. 89, South Shields C.B. 30, Seaham U.D. 26, Gateshead C.B. 21), London 87 (Hackney 35, Southwark 10), Yorkshire West Riding 85 (Pontefract M.B. 43, Castleford U.D. 14, Leeds C.B. 13), Northumberland 50 (Bedlingtonshire U.D. 16), Surrey 49 (Banstead U.D. 26), Leicestershire 40 (Leicester C.B. 27), Norfolk 31 (Ipswich C.B. 16), Glamorganshire 29 (Cowbridge R.D. 24), Cheshire 20 (Stockport C.B. 16), and Yorkshire North Riding (Middlesbrough C.B. 19).

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in March was 114, compared with 117 (revised figure) in the previous month and 118 in March, 1954.

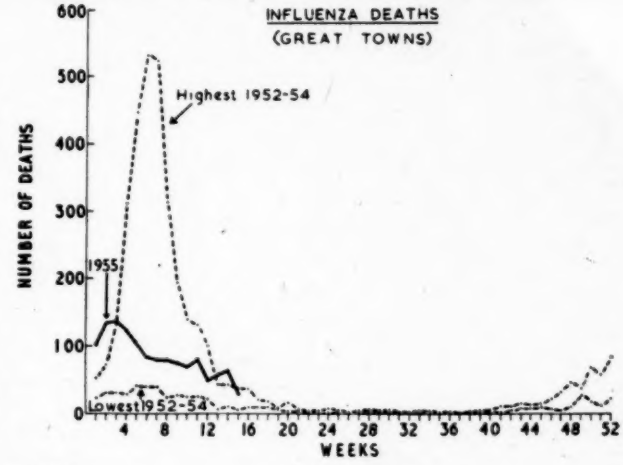
The numbers of cases of industrial diseases in the United Kingdom reported during March, 1955, were as follows: lead-poisoning 8, compressed air illness 2, anthrax 3, epitheliomatous ulceration 13, chrome ulceration 16; total 42. There was 1 death due to compressed air illness.—*Ministry of Labour Gazette*, April, 1955.

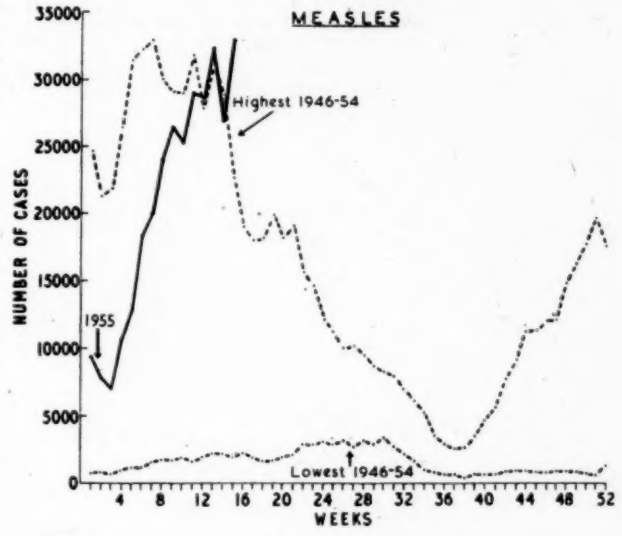
Week Ending April 23

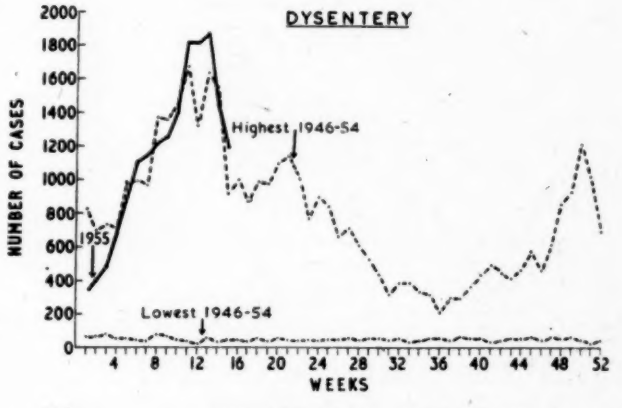
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 467, whooping-cough 1,658, diphtheria 14, measles 28,425, acute pneumonia 688, acute poliomyelitis 6, dysentery 1,053, paratyphoid 15, and typhoid fever 3.

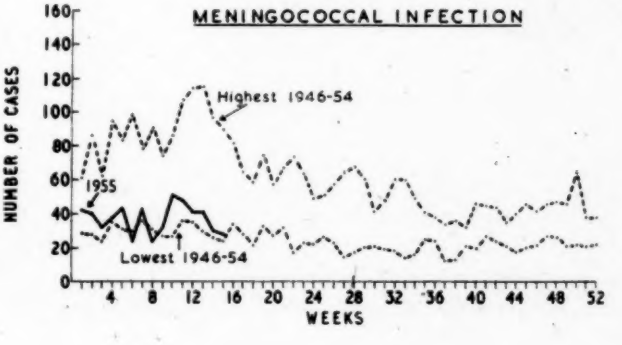
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases (deaths for influenza) of certain diseases notified weekly in England and Wales (great towns for influenza). Highest and lowest figures reported in each week during the nine years 1946–54 (influenza, 1952–4) are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Medical News

British Trial of Poliomyelitis Vaccine.—Preparations for the British trial of poliomyelitis vaccine (see *Journal*, April 30, p. 1103) are continuing pending further information from America about the cases of poliomyelitis in children inoculated with Salk vaccine. In a Press statement on May 4 the Medical Research Council stated that a member of the Council's staff was proceeding immediately to the U.S.A. to obtain first-hand information. This should be available before the routine safety tests on the present batches of vaccine in Britain are completed, and therefore before the proposed British trial is due to begin. A dispatch from the New York correspondent of *The Times*, dated May 1, states that 29 cases of poliomyelitis occurred last week in the United States in persons inoculated with Salk vaccine, all but three of whom had received the vaccine prepared by the Cutter laboratories of Berkeley, California. As a result, the use of the Cutter vaccine has been banned and California has suspended its inoculation programme until the investigation of the cases is complete. The possible causes of the American setback are discussed elsewhere in the *Journal* (p. 1144). Meanwhile in Britain negotiations continue with the Government of India to relax the ban on the export of monkeys. The M.R.C. has also sent a member of its staff, Dr. F. KINGSLEY SANDERS, to the M.R.C. field station at Fajara in the Gambia to investigate the possibility of arranging regular supplies of monkey kidneys from there. The financial implications of the American demand for the Salk vaccine have been agitating Wall Street, according to reports of an article in the *New York Post*. This source says that the American firms producing the vaccine are expected to make $20m. profit this year, and is quoted as saying, "Sharp-eyed investors already have made an impressive killing on the vaccine." The report adds that Dr. Salk draws no royalties.

Edinburgh Medical Exhibition.—Declaring open the "Edinburgh Medical Exhibition" at the Assembly Rooms, Edinburgh, on April 25, Professor D. M. DUNLOP reminded his audience that the remarkable therapeutic advances of the past 50 years had been largely due to the close co-operation between the medical profession and the pharmaceutical industry. Not only had the industry developed the fundamental discoveries of university research workers such as Ehrlich, Minot, and Fleming, but it had itself contributed many discoveries such as cyanocobalamin and the new antimalarials. Professor Dunlop complimented the industry on marketing drugs which are amongst the lowest-priced in Europe, despite rising wages, the increased cost of plant and buildings, and an annual expenditure on research estimated to exceed £3m. Too rigid a bureaucratic control on the price of drugs might prove disastrous to the pursuit of pharmaceutical research and to the industry's exports, which had increased in value from under £2m. in 1938 to over £33m. in 1954. The manufacturers of "ethical" products, continued Professor Dunlop, had through their advertising an influence on medical practice much more potent than that of "the bleatings of professors of therapeutics." Such an influence carried with it great responsibilities. It was not particularly ethical, he thought, to market, for example, expensive tonics, capsules of the vitamin-B complex in a country where beriberi and pellagra are practically unknown, and polyglandular pills. The last was a return to the medicine of savages "who believe that if you eat the heart of a lion you will grow strong." Professor Dunlop concluded by declaring it a privilege to open an exhibition of great interest and educational value, an expression of the splendour of modern therapeutic advance.

Bart's Linear Accelerator.—Last October we reported the completion of the Mullard 15 million volt linear accelerator at St. Bartholomew's Hospital, London (see *Journal* of October 2, 1954, p. 819). On April 27 the accelerator was officially inaugurated by the DUKE OF GLOUCESTER, president of the hospital. The machine, costing over £50,000 and paid for from the hospital's endowment funds, with its combination of high energy and high intensity of radiation is the most powerful therapeutic apparatus to be installed in any hospital in Britain. The accelerator will be used primarily for fundamental research on the action of radiations on living tissue, and secondly for treatment. For the latter, besides high energy *x* rays, the machine can produce electrons and also, by bombarding uranium, neutrons. It is proposed to investigate the possibilities of both electron and neutron therapy. Electron therapy has the advantage of limited penetration (about 3 in.—7.6 cm.), while neutron therapy may differ entirely from conventional *x*-ray therapy. For the present, the accelerator is being housed near the physics department under the direction of Professor J. ROTBLAT.

Dr. G. W. Corner, director of the department of embryology at the Carnegie Institute of Washington, has been elected a Foreign Member of the Royal Society "for his work on the endocrine control of gestation, and especially on the function of the corpus luteum in mammals."

Royal College of Surgeons.—At the Council meeting on April 21 Mr. WILLIAM DOOLIN (Dublin) and Professor ROBERT JANES (Toronto) were admitted Honorary Fellows, and Professor G. J. CUNNINGHAM (London) Sir William Collins Professor of Human and Comparative Pathology and Conservator of the Pathological Museum. *Jacksonian Prize.*—Last year's prize was awarded to Mr. CECIL W. D. LEWIS (Cardiff) and a certificate of honourable mention to Dr. OLIVER C. LLOYD (Bristol) for their essays on "Melanomas and Melanosis." The subject for the 1956 prize will be "Portal Hypertension." *John Hunter Medal and Triennial Prize.*—These were awarded to Professor STEPHEN L. BAKER (Manchester) "for his outstanding contributions to the study of bone structure and disease." *Mitchiner Medal.*—The 1955 medal was awarded to Colonel W. R. M. DREW, late R.A.M.C., "for his distinguished contributions to medicine in the Army, with special relation to the teaching of tropical medicine."

Jessie Macgregor Prize.—The Royal College of Physicians of Edinburgh announces that an award of the Dr. Jessie Macgregor Prize for Medical Women (value £75) will be made in July to the applicant presenting "the best record of original work in the science of medicine." Applicants must be medical graduates of Edinburgh University or holders of the Scottish Triple Qualification, and applications, marked "Dr. Jessie Macgregor Prize," must reach the Convener of Trustees, Royal College of Physicians of Edinburgh, 9, Queen Street, Edinburgh, 2, not later than June 30.

Clinical Evening for G.P.s.—The London Hospital held its second clinical evening for local general practitioners on April 27, when cases were demonstrated by members of the medical and surgical staff. A large number of practitioners took advantage of the opportunity to meet their hospital colleagues and attend the clinical demonstrations. Light refreshments were provided beforehand. The evening was an obvious success: as a member of the staff put it, "I don't know why we didn't do this years ago." The guest practitioners, for their part, were clearly most appreciative of the teaching hospital's gesture.

Agricultural Pesticides.—The spraying season is now in full swing. An article describing the toxic hazards of the more dangerous selective weed-killers and insecticides was printed in the *Journal* of April 2 (p. 841). Treatment was fully discussed and an appendix stated where samples of oxalated blood should be sent for D.N.C. and cholinesterase estimations, and gave technical details of their collection. In addition to certain named laboratories in Lewisham, Portsmouth, Peterborough, and Worcester, specimens may be

sent to the hospital laboratory normally used for pathological tests of any kind.

British Association of Physical Medicine.—The following officers for 1955–6 were elected at the annual meeting on April 23: *President,* LORD HORDER; *vice-president,* Dr. W. S. TEGNER; *hon. treasurer,* Dr. A. C. BOYLE; *hon. secretary,* Dr. G. O. STOREY; *hon. editor,* Dr. H. A. BURT.

COMING EVENTS

Society for Endocrinology.—Dr. A. LACASSAGNE (Paris) will lecture on "Endocrine Factors Concerned in the Genesis of Experimental Mammary Carcinoma" at the Royal Society of Medicine, May 24, at 5 p.m. Non-members welcomed. Admission free, without ticket.

Institute of Hospital Administrators.—Annual Conference at the Caxton Hall, Westminster, May 12–14. Details from the secretary of the Institute, 75, Portland Place, London, W.1.

Society for Applied Bacteriology.—Summer conference and annual meeting at Cambridge, July 4–6, open to non-members. Symposium on "Food Microbiology and Public Health." Details from Mr. G. SYKES, Boots Pure Drug Co., Ltd., Microbiology Division, Nottingham.

NEW ISSUES

Medical and Biological Illustration.—The next issue (Vol. 5, No. 2) is now available. The contents include:

DIRECT KINERADIOGRAPHY ON 35 MM. FILM AND ONE APPLICATION IN BIOLOGICAL RESEARCH. P. Thevenard.
CAMERA LUCIDA TRACINGS IN MEDICAL RESEARCH. S. Engel.
THE PHOTOGRAPHY OF GROSS SPECIMENS WITH FLUORESCENT LIGHTING. T. N. Salthouse.
A NEW MUSEUM OF CARDIAC PATHOLOGY. Reginald Hudson.
THE CYCLOSTEREOSCOPE. François Savoye.
A SIMPLE LIGHT INTEGRATING METER FOR USE WITH FLASH TUBES. R. D. Moore.
EQUIPMENT AND METHODS.

Issued quarterly: annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 9

EDINBURGH UNIVERSITY.—At West Lecture Theatre, University New Buildings, 5 p.m., Dr. D. J. Guthrie: Medicine Becomes Anatomical.
INSTITUTE OF CARDIOLOGY.—9.30 a.m., Sir John Parkinson: Diseases of the Aorta.
LONDON UNIVERSITY.—At Wright-Fleming Institute Lecture Theatre, St. Mary's Hospital Medical School, 5 p.m., special university lecture in medicine by Professor F. D. Moore (Harvard): Endocrinology and Metabolism in Surgical Care: (1) Metabolic Observations.
MEDICAL SOCIETY OF LONDON.—8.30 p.m., second general meeting; 8.45 p.m., Annual Oration by Dr. Macdonald Critchley: Verbal Symbols in Thought.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. R. I. S. Bayliss: Infantilism and Dwarfism.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Dr. DeWitt H. Smith: Ballistocardiography.

Tuesday, May 10

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. C. Wells: Disorders in Pigmentation.
LONDON UNIVERSITY.—At King's College, 5.30 p.m., special university lecture in biophysics and microbiology by Dr. Harriett Ephrussi-Taylor (Paris): Induced Transformations of Bacteria: The Nature of Transformation and the Factors Involved.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Arnott Demonstration by Dr. H. J. Hoffmann: Innervation of Voluntary Muscle.
ST. ANDREWS UNIVERSITY.—At Department of Medicine, Queen's College, Dundee, 2.30 p.m., discussion to be opened by Mr. A. Logan, Dr. R. D. Marquis, and Professor D. M. Douglas: Consideration of Aortic Stenosis and its Surgical Treatment.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.15 p.m., Cushny Memorial Lecture by Dr. Mary Pickford: Antidiuresis.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., neurological demonstration by Dr. T. Rowland Hill.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., Almroth Wright Lecture by Dr. D. A. Long: Response of the Host to Bacterial Infection.

Wednesday, May 11

BIRMINGHAM UNIVERSITY: FACULTY OF MEDICINE.—At Large Anatomy Theatre, 4 p.m., Leonard Parsons Memorial Lecture by Professor Wilfrid Gaisford: Protection of Infants Against Tuberculosis.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Pathogenesis of Fungous Infections of the Skin.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. P. Lee Lander: Prognosis in Bronchiectasis.
LONDON UNIVERSITY.—(1) At Wright-Fleming Institute Lecture Theatre, St. Mary's Hospital Medical School, 5 p.m., special university lecture in medicine by Professor F. D. Moore (Harvard): Endocrinology and Metabolism in Surgical Care; Application in Daily Care. (2) At King's College, 5.30 p.m., special university lecture in biophysics and microbiology by Dr. Harriett Ephrussi-Taylor (Paris): Induced Transformations of Bacteria: Kinetic Study of the Transformation Process.
MEDICAL RESEARCH COUNCIL.—At National Institute for Medical Research, The Ridgeway, Mill Hill, N.W., 5 p.m., Dr. Emil L. Smith (University of Utah): Chemistry of Antibodies and Gamma Globulins.
MIDDLESEX COUNTY MEDICAL SOCIETY.—At Harefield Hospital, 3 p.m., Mr. T. Holmes Sellors: Cardiac Surgery To-day; Dr. E. Idris Jones: Eosinophilic Lung; Dr. J. C. Roberts: Some Observations on Unilateral Emphysema and Bronchiectasis; Mr. J. W. Jackson: Modified Thoracoplasty.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor G. Payling Wright: General Pathology of Tuberculosis (II).

Thursday, May 12

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, W., 8 p.m., Dr. W. P. Berrington: Fugue States.
BIRMINGHAM UNIVERSITY: FACULTY OF MEDICINE.—At Large Anatomy Theatre, 4 p.m., Leonard Parsons Memorial Lecture by Professor Wilfrid Gaisford: Protection of Infants Against Tuberculosis.
DUBLIN UNIVERSITY: SCHOOL OF PHYSIC, TRINITY COLLEGE.—At Physiology Theatre, 4.30 p.m., John Mallet Purser Lecture by Professor G. R. Cameron, F.R.S.: New Fields in Cell Pathology.
EDINBURGH UNIVERSITY.—At West Lecture Theatre, University New Buildings, 5 p.m., Dr. D. J. Guthrie: Classic Literature of Medicine.
HONYMAN GILLESPIE LECTURE.—At University New Buildings, Edinburgh, 5 p.m., Mr. G. H. Macnab: Maldescent of the Testicle.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Antibiotics.
LONDON UNIVERSITY.—At King's College, 5.15 p.m., Halliburton Lecture by Professor Igino Spadolini (Florence): Effects of the Acetylcholine-cholinesterase System on the Heart.
NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, 8.30 p.m., Dr. A. B. Kinnier Wilson: New Approach to Respiratory Poliomyelitis
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. C. L. Cope: Cortisone and A.C.T.H.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor R. V. Cooke: Advanced Carcinoma of the Colon, with particular reference to the Inflammatory Factor.
ROYAL SOCIETY.—4.30 p.m., film illustrating research activities of Istituto Superiore di Sanità, Rome, with introductory address by Director-General, Professor D. Marotta, followed by talk by Professor E. B. Chain, F.R.S.: Some Recent Advances in Carbohydrate Metabolism.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Medical School, Small's Wynd, Dundee, 5 p.m., Dr. H. Payling Wright: Thrombosis and Some Less Recognized Aspects of Anticoagulant Therapy.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration in Psychiatry.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 4.45 p.m., Professor Emil L. Smith (University of Utah): Mode of Action of Proteolytic Enzymes.

Friday, May 13

HARVEIAN SOCIETY OF LONDON.—At Royal College of Surgeons of England, 8.15 p.m., Buckston Browne Dinner.
● INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. B. F. Russell.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. J. G. Scadding.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. A. R. Dingley: Tonsillectomy in Children and Adults.
LONDON UNIVERSITY.—At King's College, 5.30 p.m., special university lecture in biophysics and microbiology by Dr. Harriett Ephrussi-Taylor (Paris): Induced Transformations of Bacteria: Confrontation of Genetic and Physico-chemical Data.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. J. H. Middlemiss: Radiology of the Acute Abdomen.
ST. ANDREWS UNIVERSITY.—At Department of Medicine, Queen's College, Dundee, 2.30 p.m., discussion to be opened by Professor E. J. Wayne and Dr. C. Pickard: Angiocardiography in Congenital Heart Disease.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Sir Heneage Ogilvie: Shock (with coloured film and sound track).
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.15 p.m., Cushny Memorial Lecture by Dr. L. E. Bayliss: Process of Secretion.
WHITTINGTON HOSPITAL.—At St. Mary's Wing (Ward D.6), 5.15 p.m., clinical pathological conference. Dr. C. G. Whiteside: Aortography in Urology.

Saturday, May 14

BIOCHEMICAL SOCIETY.—At Reading University, 11 a.m., scientific papers.
CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—10.30 a.m., Symposium: Paediatrics.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Campbell.—On April 14, 1955, at Harbour Breton, Newfoundland, to Dr. Margaret (formerly Kennedy), wife of Dr. Ronald W. Campbell a son—David Alexander Young.

Ellison.—On April 10, 1955, to Jean, wife of Dr. Stanley Ellison, of 79, Fortune Green Road, London, N.W., a sister for Beverley

Luntz.—On April 25, 1955, at Sorrento Maternity Hospital, Birmingham, to Pamela, wife of George Richard William Neal Luntz, M.R.C.P., a daughter—Verity Anne.

McCracken.—On April 28, 1955, at St. Mary's Hospital, Manchester, to Dr. Margaret (formerly Laycock) and Dr. Dermot McCracken, a son—James Justin.

DEATHS

Sankey.—On April 6, 1955, at 16, Crick Road, Oxford, Richard Harvey Sankey, M.B., B.Ch., F.F.R., aged 80.

Shafto.—On April 12, 1955, at Edinburgh, William Alexander Shafto, M.D., D.P.H., of Craigdarroch, Bo'ness, West Lothian.

Young.—On April 3, 1955, at his home, Sandrock Cottage, Westcott, near Dorking, Surrey, William Arthur Young, M.B., B.S., D.T.M.&H., formerly of Singapore, and Perth, Western Australia.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Inoculations and Poliomyelitis

Q.—*What is thought to be the mechanism by which certain inoculations predispose to the development of paralytic poliomyelitis? Is it due to a direct transfer of virus during the inoculation procedure, similar to a streptococcal cellulitis following inoculation, or is there some other mechanism?*

A.—Firstly, there is no evidence to support the view that poliomyelitis virus is transferred to the tissues from needle or syringe during the inoculation of whatever prophylactic or other substance is being injected. The evidence rather indicates that virus already present in the host is activated and localized by tissue trauma. It is known, for example, that the performance of tonsillectomies in an area where poliomyelitis is prevalent may be followed by cases of bulbar poliomyelitis, and that excessive exercise and fatigue of certain muscle groups may be associated with paralytic poliomyelitis in these muscles. The injection of a substance likely to cause local tissue trauma and reaction—and this is most common with alum-containing prophylactics—may for the same reason help to localize poliomyelitis virus, already present in the host, to the motor cells of the central nervous system associated with the traumatized area. Therefore the intramuscular injection of prophylactics likely to cause some degree of local reaction may have to be temporarily discontinued in an area where poliomyelitis has become prevalent.

Neurological Effects of Chronic Carbon Monoxide Poisoning

Q.—*I have a patient who has been diagnosed as suffering from disseminated sclerosis. For a long time prior to and during the early part of his illness he was employed at a gas works, and several doctors have expressed the opinion that chronic carbon monoxide poisoning might have initiated the disease. Another person working in the same place for a time exhibited, broadly speaking, the same symptoms. Is it thought that continual exposure to carbon monoxide can ultimately produce sclerotic lesions in the nervous system, and, if so, where are references to be found in medical literature?*

A.—There is no evidence that chronic carbon monoxide poisoning can lead either to the clinical manifestations or to the histological changes of disseminated sclerosis. From experimental data it appears that the chronic stages of degeneration are of the same order and situation as those found in acute poisoning, and principally affect the neurones of the cerebral cortex and corpus striatum. While variable degrees of Parkinsonism may be observed clinically, a wide variety of minor neurological disturbances have also been recorded in numerous reports. These, and a detailed personal investigation into the problem of chronic carbon monoxide poisoning as an industrial hazard, have been published as a monograph by Aage Grut (Copenhagen, 1949). Two cases in which cerebral subcortical myelinopathy was attributed to carbon monoxide poisoning have been reported also by Hsü and Ch'eng.[1] Since the lesions here involved the white matter these cases are of greater interest in relation to the present query. But neither the histology nor the recorded neurological disturbances in these two subjects suggest any affinity with disseminated sclerosis. It seems most likely that the cases mentioned in the question were coincidental.

REFERENCE
1. *Brain*, 1938, **61**, 384.

Dreams

Q.—*What is the cause of excessive dreaming? Can any treatment be given to prevent it? Is it true that dreaming occurs in the penultimate seconds of sleep? A patient of mine, aged 28, is pregnant for the second time. She has always had vivid dreams, but during her first pregnancy, and so far during her second, she has dreamt every night, and her dreams have been of such startling reality and apparently of such great length that she wakes up unrefreshed from her night's sleep. There is no evidence of any psychiatric abnormality.*

A.—Excessive dreaming—that is, dreaming more than is customary for a particular individual—comes from unconscious—that is, unrecognized—emotional stress. The already vivid dreams of this patient may well have been intensified in consequence of emotions associated with her pregnancy. Dreams are the experience of everyone and are not symptoms of a disorder. Their vehemence can best be modified by discussing them with a psychotherapist, as the appreciation of a dream's significance renders its repetition unlikely. Dream activity can be reduced and often eliminated by the use of hypnotics.

There is no evidence that dreaming always occurs just before waking. Thus sleep-walkers and talkers may subside into tranquil slumber without waking up. Probably we dream all night, but remember only fragments; thus the train of thought during the day will often revive a forgotten dream.

Aetiology of Peptic Ulcer

Q.—*What are the latest views on the aetiology of peptic ulceration?*

A.—The short answer, and probably the most correct one, is that we do not know the cause of peptic ulceration. There are, however, a few clues to the aetiology which may prove to be of value.

In the first place, it is probably necessary to consider gastric ulcer and duodenal ulcer separately. Although the two types of ulcer are practically indistinguishable clinically and are treated in much the same way, and although they are found in association with one another more often than would be expected by chance, there are many reasons for thinking that their causes are not identical. Both types of ulcer are to some extent hereditary—that is to say, they occur more commonly among members of the families of ulcer subjects than in the general population—but the hereditary susceptibility is expressed relatively seldom, and the environmental factors which determine whether or not a person has an ulcer are extremely important. (See *British Medical Journal*, 1954, **2**, 315.)

Recent evidence bearing out the role of heredity has been obtained by Professor Aird and his colleagues at the British Postgraduate Medical School who have shown that both types of ulcer—but perhaps more particularly duodenal ulcer—are commoner in persons of Blood Group O. This is not surprising when it is recalled that blood group substances occur in the gastro-intestinal secretions, and it is therefore understandable that they may play a part in protection against autodigestion.

The importance of environmental factors is shown by the great changes in prevalence which have taken place over the last half-century. Duodenal ulcer has become much commoner, while gastric ulcer, which was characteristically a disease of young women, is now predominantly a disease of the middle-aged.

Duodenal ulcer is rare in childhood, but when it occurs it affects both sexes equally. It begins to be common after puberty, and subsequently is four to six times commoner in men than in women. It is approximately equally distributed among all sections of the community. Duodenal ulcers nearly always occur in association with an increased amount of gastric secretion, which would appear to be the result of an increased number of oxyntic cells in the mucosa. Why there should be more oxyntic cells is not known; one theory is that they reflect a work hypertrophy,

in which the stimulating factor is a food substance or chemical added in food processing. Psychological factors are probably of less importance than was thought 10 years ago. There is no doubt that anxiety or mental conflict may exacerbate symptoms of ulcer or bring on a complication; but the evidence that a particular personality, or type of emotional stress, is the primary cause of duodenal ulcer is not impressive.

Gastric ulcer shows a less marked male preponderance and it does not become common until later—that is, until after the age of 35 years. It is rare among the wealthy and becomes increasingly common as the social scale is descended. In this its distribution is reminiscent of gastric cancer. Gastric ulcer occurs characteristically in persons whose gastric secretion is normal or diminished, but it is doubtful if it ever occurs in persons whose stomachs are persistently achlorhydric. In the light of present knowledge it may be thought of as due to "wear and tear."

Nausea after Morphine

Q.—*What is the best way of dealing with nausea and vomiting following the administration of morphine for pain relief? Are nalorphine, antihistamines, or sedatives helpful?*

A.—There are two ways of dealing with the nausea and vomiting. When the morphine has been given and has produced these symptoms they can be arrested by the administration of nalorphine. This will, however, abolish the analgesia also. The better method is to try a different analgesic, for there are great variations in the way they are tolerated. Amidone is rather stronger than morphine, and is given in about three-quarters the dose. Pethidine is weaker and is given in about eight times the dose. Phenadoxone (by injection) is stronger and is given in three-fifths the dose. In using analgesics the attempt should be made to find which suits the patient best: what suits one may not suit another. On the whole it seems to be true that morphine produces nausea and vomiting more often than the other analgesics mentioned. The article by P. W. Nathan[1] should be consulted.

REFERENCE
[1] *British Medical Journal*, 1952, **2**, 903.

Epidermolysis Bullosa

Q.—*Would you please tell me if there is any efficient form of treatment for epidermolysis bullosa in an 8-months-old infant? The symptoms, affecting her buttocks, shoulders, back of neck and head, finger-tips, and centre of upper lip, appeared soon after birth.*

A.—The baby is probably suffering from the recessive hypoplastic type of epidermolysis bullosa which appears at birth or soon after. Bullae may arise spontaneously on any part of the skin, but especially at the sites of pressure or trauma. The mucous membranes are usually affected.

The outlook is gloomy and few patients reach puberty. If they do it is possible that some improvement may take place, but it is likely that treatment with plastic surgery will be required, such as to correct the binding together of the fingers. No treatment is known which affects the condition, and this, of course, is true of most congenital defects. Cortisone is not beneficial. Antibiotics are only helpful in the treatment of secondary infection of the raw areas. It is necessary to wrap the baby in cotton-wool so that all surfaces liable to injury are protected.

Cyanosis of Lips in Acrocyanosis

Q.—*Is cyanosis of the lips a common concomitant of acrocyanosis? My patient, a little girl aged 4½, shows a constant bluish tinge of her lips, summer and winter. She appears to be perfectly healthy, and, apart from the fact that she tends to suffer from acrocyanosis in the winter, shows no evidence of organic disease on clinical examination. What might be the aetiology of this condition, and what possibilities ought one to exclude?*

A.—Hands and feet are dominantly affected by acrocyanosis. The condition is due to dilatation and sluggish circulation in the small vessels and venules, and cyanosis is exaggerated in cold weather. The lips are not involved. In judging cyanosis of the lips it should be remembered that there is often some pigmentation on the outer edge of the lips, which may be deceptive. When the interior of the lip is inspected in such cases no cyanosis is seen.

Cyanosis due to congenital heart disease is accompanied by some degree of polycythaemia and finger-clubbing, and it should be remembered that the cardiac physical signs of congenital cyanotic heart disease may be minimal. Methaemoglobinaemia gives a leaden hue to those parts of the skin and mucous membranes where the colour of the blood is visible. Remarkable improvements in colour may follow the oral administration of a large dose of ascorbic acid. Methaemoglobin is recognized by spectroscopic examination of the blood.

Frigidity after a Difficult Labour

Q.—*A young married couple are worried by frigidity in the wife since the birth of their first child after a difficult labour. Previously the wife was passionate and achieved orgasm easily, but now, although allowing intercourse, she is not roused by it. She realizes that fear of another difficult labour may have played a part in the first few months after the birth of the baby, but that was two years ago, and she thinks that she has now got over this. The couple practise contraception with a Dutch cap, and owing to the husband being away at sea intercourse is necessarily infrequent.*

A.—An organic basis for the frigidity is unlikely, although overstretching or tearing of the vagina during delivery could diminish stimulation and therefore satisfaction during coitus. However, reduction in sexual feelings after pregnancy, and especially the first pregnancy, is the experience of most women. The fact that a fundamental objective of coitus has been achieved; the awakening of mother love with some readjustment of the affections; the extra work, anxiety, and responsibility of looking after the child—all play a part. This reaction, however, is usually only temporary and clears up as the period of nervous strain passes, as physical well-being returns, and as the baby begins to show signs of independence. Two years is rather long for this mechanism to continue to operate, although in this case it may be fostered and extended by the frequent and prolonged absences of the husband. Separation means that the woman must deliberately stifle her sex feelings and learn to live without coitus. She may therefore look more and more to the child as an outlet for her emotions and affection, and this is even more likely if she has decided not to conceive again because of her previous obstetrical experience. Despite the passage of time, fear of another pregnancy must also rank high in the list of possible causes of frigidity. The woman might also have a fundamental objection to contraception, and this could arouse an inner conflict between desire for, and fear of, pregnancy. Is it not possible for the difficulty which occurred in the last pregnancy to be avoided in the next, and could the couple be reassured on this point with a hope of them then being able to take a more normal outlook on married life and the production of a family?

Treatment of Diverticulosis

Q.—*What dietetic or other regime is indicated in a case of diverticulosis of the transverse colon discovered by barium follow-through? The patient was referred to the radiologist on account of occasional discomfort around the left costal margin.*

A.—It is customary in cases of diverticulosis to prescribe a diet from which articles of food known to leave a high residue are excluded, the so-called non-roughage diet. Cellulose residues from green leafy vegetables and fruits, especially uncooked, wholemeal bread, and so on are the chief offenders. The absence of roughage tends to induce constipation which can to some extent be overcome by an adequate fluid intake and by the administration of plain "petrolagar emulsion" in small doses with each meal. It

must be remembered that there is no musculature in the wall of the diverticulum, so that if it becomes filled with inspissated faecal material it cannot empty itself: the colonic contents should therefore be kept, so far as possible, soft and moist.

In the absence of inflammation pain is due to the associated colonic spasm, so in an attack the administration of bowel antispasmodics is often valuable. Ordinary purges should be avoided, since they tend to increase spasm, but an occasional Studa chair colonic wash-out, say once a month, may be well worth a trial. On a simple regime such as this many cases of diverticulosis carry on for a great number of years without any serious complication arising.

Shoes for Patients with Pes Cavus

Q.—*I think that those who suffer from the common condition of pes cavus are less disabled if they can obtain shoes that fit. Do you agree? If so, can you tell me of any firm that provides suitable shoes? Hand-made shoes are too expensive for most patients, and I do not think every patient is willing to get his shoes through an orthopaedic clinic. So far as I can tell the local shops can only provide shoes for "standard" feet.*

A.—I entirely agree that to be comfortable with pes cavus shoes must fit. Unfortunately no firm provides suitable shoes. There are no alternatives to having hand-made shoes or surgical shoes obtained from the National Health Service.

Sometimes such people can get along with wide toe-capped shoes and a firm pad under the arch.

Sulphathiazole

Q.—*According to certain publications, principally North American, sulphathiazole should not be used on account of its greater toxicity; according to others sulphathiazole is still a useful drug in many cases, as it is the most active of the sulphonamides and in certain cases the toxic effects are insignificant. What are your expert's views on this?*

A.—Although sulphathiazole is a highly active sulphonamide it is a very insoluble one and is particularly likely to cause renal irritation, and even in some cases urinary suppression. Such dangers can usually be easily guarded against in temperate and cold climates, where most of the fluid output is through the kidneys, by ensuring a really adequate intake of fluid whenever sulphathiazole is given; but in warm climates, where perspiration may be excessive and where even with care the urinary output may not be adequate in fevered conditions, sulphathiazole undoubtedly possesses serious drawbacks. It is very doubtful if the more modern and much more soluble sulphonamides such as sulphadimidine are any less active than sulphathiazole.

Epilation

Q.—*Which method of epilation of facial and body hair is preferable—galvanic or diathermy—and why? Should a local analgesic be used before epilation? Does the epilation leave any scarring afterwards and, if so, can it be prevented?*

A.—The choice between electrolysis and diathermy is a matter of personal preference, and in the opinion of the writer, who has used both, there is really little to choose between the two. The apparatus for electrolysis is less expensive, and it is probably easier through faulty technique to cause scarring with diathermy than it is with electrolysis. For these two reasons electrolysis is perhaps preferable. Local analgesia is not usually given; some patients complain of pain, and a local analgesic is then advisable provided the area to be treated is not too large.

Of course, the object of epilation is to destroy the hair follicle permanently without the production of a scar, and the skill in treatment lies in passing the current for the right length of time and at the right intensity. When the current has passed long enough the hair will come out with very gentle traction, and there may be a slight white opacity of the skin extending for a distance of a fraction of a millimetre around the follicle. Any area of necrosis which is wider than this is excessive and is liable to be followed by visible scarring. It is, of course, better to err on the side of under-treatment rather than over-treatment, which would result in scarring; the operator soon gets to know how long to leave the current on in the precise conditions in which he is working. A practical demonstration with the apparatus to be used would be very valuable for anybody intending to undertake this treatment for the first time.

"Cracking in the Head"

Q.—*I should be grateful if you could kindly throw a little light on the following case. The patient is a rather senile lady of 77 who has a well-compensated mitral valvular disease. Her principal complaint is of a "cracking in the head" which is accompanied by a sudden severe pain and often followed by flushing of the face. She has phases when she is withdrawn and others when she is full of complaint and worrying about herself, and in the absence of physical findings I was inclined to the view that the "crackings" were neurotic in origin. However, recently both her husband and her daughter have heard the cracks, though they have not told her so. Her daughter, who is a very sensible and competent woman, likens the sound exactly to that of "knuckle cracking." The attacks occur many times a day and are very distressing.*

A.—Audible cracking like knuckle cracking is almost certainly produced in a joint. Cracking in the temporomandibular joint is a very familiar phenomenon. In elderly and particularly edentulous patients the chewing movements may force the head of the mandible back on to the anterior surface of the external meatus, and pressure here may produce pain referred to the face.

Chronic Alcoholism and Fertility

Q.—*What effect has chronic alcoholism on fertility? What is the mechanism for any adverse effect?*

A.—It is generally accepted that chronic alcoholism can lead to male infertility by interfering with sperm production. It is most probable that the effect is a direct toxic one on the germinal epithelium, leading to partial or complete failure of spermatogenesis. Since chronic alcoholism is a good deal less frequent in women than in men, its effects on female infertility are less well recognized. It can, however, bring about amenorrhoea, either as a result of a direct toxic action on the ovaries or perhaps more likely through disturbance of the pituitary–ovarian relationship.

Correction.—The penultimate sentence in the first paragraph on p. 871 of the paper by Dr. C. D. R. Pengelly on "Pneumococcal Meningitis" (*British Medical Journal*, April 9, p. 870) should have read, "Only three recoveries occurred in 16 patients in the latter group (81% mortality)." Later on the same page the paragraph beginning "The additional therapy in Group 3 . . ." should have had the words "with chloramphenicol (orally) in two and" inserted before the words "with intrathecal streptomycin in one."

Books of "Any Questions?"—The second and third volumes of "Any Questions?" are available, price each 7s. 6d. (postage 6d.), from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller. Each contains some 200 selected expert answers, and the third volume a cumulative index to the three published books.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.